Drug Class Review

Nasal Corticosteroids

Final Report Update 1

June 2008

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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INTRODUCTION

Allergic rhinitis is a condition characterized by sneezing, watery rhinorrhea, nasal itching, congestion, itchy palate, and itchy, red, and watery eyes.[1] The prevalence of allergic rhinitis has increased significantly over the last 15 years and the disease currently affects twenty to forty million Americans.[2] It is estimated that in 2002, approximately 14 million medical office visits were attributed to allergic rhinitis.[2] Many suffering from allergic rhinitis are children and young adults, whom, if treated early, may avoid later stage complications.[3] If left untreated, this condition could lead to the development or worsening of comorbidities including chronic or recurrent sinusitis, asthma, otitis media, an respiratory infections.[4, 5] Moderate to severe allergic rhinitis may also lead to sleep disorders, fatigue, and learning problems.[3, 5]

Rhinitis can be divided into 2 broad categories: allergic and non-allergic. Allergic rhinitis consists of seasonal and perennial rhinitis. Seasonal allergic rhinitis, also called hay fever, is characterized by symptoms that occur in response to specific seasonally occurring allergens. Allergens may include pollen from trees, grasses, and weeds. Perennial allergic rhinitis occurs throughout the year and is caused by allergens such as house dust mites, animal dander, cockroaches, and molds. In some geographic locations, pollen can play a role in perennial rhinitis. Patients are often sensitized to both seasonal and perennial allergens, which can be termed mixed allergic rhinitis.[6]

There is a prominent genetic component involved in the development of allergic rhinitis. Individuals with both parents suffering from atopic disease have a 50% or greater chance of affliction with allergic disease.[5] The symptoms of allergic rhinitis are caused by an IgE-mediated immune response to a particular allergen. An antibody, called immunoglobulin E (IgE), represents a major component of this immunologic reaction. The binding of the allergen to IgE molecules leads to a chain of events that includes the release of mediators such as histamine and leukotrienes and culminates in the arrival of inflammatory cells to the region. These inflammatory cells are responsible for the clinical symptoms of allergic rhinitis.

In contrast, non-allergic rhinitis is often a diagnosis of exclusion and represents a diverse group of disorders. There are several different types of non-allergic rhinitis: drug induced, gustatory, hormonal, infectious, non-allergic rhinitis with eosinophilia syndrome, occupational, anatomic, and vasomotor.[7] A classification according to the presence or absence of inflammatory cells in nasal scrapings has also been suggested in order to find the most effective treatment.[8] The symptoms of non-allergic rhinitis are similar to allergic rhinitis and include nasal obstruction, rhinorrhea, and congestion. Nasal itch and conjunctival irritation may be less with non-allergic compared with allergic rhinitis.[5]

There are several types of treatments available for allergic and non-allergic rhinitis. Allergen avoidance is not always possible for patients with allergic rhinitis. These patients can use oral or nasal antihistamines and decongestants without a prescription. Nasal mast cell stabilizers, oral leukotriene modifiers, anticholinergic nasal spray, systemic and nasal corticosteroids, anti-IgE monoclonal antibodies, and immunotherapy can be obtained with a prescription from a healthcare provider. Treatment for non-allergic rhinitis focuses on symptom management and includes several of the aforementioned medications.

Nasal corticosteroids are a safe and effective treatment option for both allergic and non-allergic rhinitis. There are currently 8 different nasal corticosteroid preparations on the U.S. market (Table 1). The nasal sprays differ with respect to delivery device and propellant, as well as potency and dosing frequency. When used daily, nasal corticosteroids significantly reduce nasal congestion, sneezing, rhinorrhea, and other symptoms.[6]

Overall, the nasal preparations are well tolerated and patients experience few, if any, adverse effects. These include nasal irritation, nasal dryness, mild to moderate epistaxis, transient headache, and dizziness. More serious adverse effects include local fungal infections, potential growth inhibition, hypothalamic-pituitary-adrenal suppression, and ophthalmologic adverse effects, including cataract.

Table 1. Nasal corticosteroid FDA-approved indications and recommended doses

Generic name	Trade name	Nasal polyps	Nonallergic (vasomotor) rhinitis	Perennial AR	Seasonal AR	Dosage in adults	Dosage in children
Beclomethasone	Beconase AQ® (42 mcg/spray)	X[a]	X	X	X	1-2 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day	6-12 yrs old: 1 spray EN 2x/day Maximum dose: 2 sprays EN 2x/day
Budesonide	Rhinocort Aqua®[b] (32 mcg/spray)			X	X	1 spray EN 1x/day Maximum dose: 4 sprays EN 1x/day	≥ 6 yrs old: 1 spray EN 1x/day Maximum dose <12 yrs old: 2 sprays EN 1x/day
Ciclesonide	Omnaris® (50 mcg/spray)			X	X	2 sprays EN 1x/day Maximum dose: 2 sprays in each nostril (200 mcg/day)	≥6 yrs seasonal AR: 2 sprays EN 1x/day; Maximum dose: 2 sprays EN (200 mcg/day) ≥12 yrs perennial AR: 2 sprays EN 1x/day Maximum dose: 2 sprays EN (200 mcg/day)
Flunisolide	Generic flunisolide (25 mcg/spray) Nasarel® (29 mcg/spray)			X	X	2 sprays EN 2x/day; may increase to 2 sprays EN 3x/day Maximum dose: 8 sprays EN/day	6-14 yrs old: 1 spray EN 3x/day or 2 sprays EN 2x/day Maximum dose: 4 sprays EN 1x/day
Fluticasone furoate	Veramyst® (55 mcg/spray)			X	X	2 sprays EN 1x/day may decrease to 1 spray EN 1x/day once maximum benefit is achieved and symptoms are controlled	2 to 12 yrs: initial, 1 spray EN 1x/day; if adequate response is not achieved, may increase to 2 sprays EN 1x/day; reduce dosage to 1 spray EN 1x/day once maximum benefit is achieved and symptoms are controlled ≥12 yrs: 2 sprays EN 1x/day; may decrease to 1 spray EN 1x/day once

Generic name	Trade name	Nasal polyps	Nonallergic (vasomotor) rhinitis	Perennial AR	Seasonal AR	Dosage in adults	Dosage in children
							maximum benefit is achieved and symptoms are controlled
Fluticasone propionate	Generic fluticasone (50 mcg/spray) Flonase® (50 mcg/spray)		X	X	X	2 sprays EN 1x/day or 1 spray EN 2x/day Maximum dose: 2 sprays EN 1x/day	≥4 yrs old: 1 spray EN 1x/day Maximum dose: 2 sprays EN 1x/day
Mometasone	Nasonex® (50 mcg/spray)	x (≥18 years old)		X	X[c]	2 sprays EN 1x/day Nasal polyps: 2 sprays EN 2x/day	(2-11 years old): 1 spray EN 1x/day
Triamcinolone	Nasacort AQ® (55 mcg/spray)			X	X	2 sprays EN 1x/day Maximum dose: 2 sprays EN 1x/day	6-11 yrs old: 1 spray EN 1x/day Maximum dose: 2 sprays EN 1x/day

[a] Indicated for the prevention of recurrence of nasal polyps following surgical removal.
[b] FDA pregnancy category B, all others category C.
[c] Treatment and prophylaxis: Prophylaxis of seasonal allergic rhinitis with mometasone (200 mcg/day) is recommended 2-4 weeks prior to anticipated start of pollen season.
EN= each nostril; AR= allergic rhinitis
Data source: Micromedex

Scope and Key Questions

The purpose of this review is to help policy makers and clinicians make informed choices about the use of nasal corticosteroids. Our goal is to summarize comparative data on efficacy, effectiveness, tolerability, and safety.

Report authors drafted preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by the Washington State Preferred Drug Program (PDP). Washington State PDP is responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The Washington State PDP approved the following key questions to guide this review:

1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

Inclusion Criteria

Population(s)

Adult patients and children (under age 18) in outpatient settings with the following diagnosis:

- Seasonal or perennial allergic or non-allergic rhinitis

Table 2. Interventions

Generic name	Trade name(s)	Forms
Beclomethasone	Beconase®, Beconase AQ®, Vancenase®, Vancenase AQ®	Nasal spray
Budesonide	Rhinocort®, Rhinocort Aqua®	Nasal spray
Ciclesonide	Omnaris®	Nasal spray
Flunisolide	Nasalide®, Nasarel®	Nasal spray
Fluticasone furoate	Veramyst®	Nasal spray
Fluticasone propionate[a]	Flonase®	Nasal spray
Mometasone	Nasonex®	Nasal spray
Triamcinolone	Nasacort®, Nasacort AQ®	Nasal spray

[a] Unless otherwise stated, fluticasone propionate is referred to as 'fluticasone' or 'fluticasone aqueous' throughout this report; fluticasone furoate is always referred to as such.

Effectiveness outcomes

- Symptomatic relief
- Onset of action

Safety outcomes

- Overall adverse effect reports
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events (localized infection of nasal mucosa, hypersensitivity, hypercorticism, HPA suppression, growth suppression in pediatric population, headache, throat soreness, dry mouth, nasal irritation)

Study designs

1. For efficacy, controlled clinical trials and good-quality systematic reviews
2. For safety, controlled clinical trials and good-quality systematic reviews and observational studies.

METHODS

Literature Search

To identify relevant citations, we searched the Cochrane Central Register of Controlled Trials (4th Quarter 2005 Update 1: 3rd Quarter 2007), the Cochrane Database of Systematic Reviews (3rd Quarter 2007), and MEDLINE (1966 to October Week 3 2005; Update 1: September Week 1 2007) using terms for included drugs, indications, and study designs (see Appendix A for complete search strategies). Our literature search was limited to English-language publications. To identify additional studies, we also searched reference lists of included studies and reviews and FDA information.[9] In addition, dossiers were requested from manufacturers of the included drugs. Dossiers were submitted by the following pharmaceutical companies: AstraZeneca (budesonide aqueous), GlaxoSmithKline (fluticasone furoate), Sanofi-Aventis (triamcinolone acetonide), and Schering-Plough (mometasone furoate).

All citations were imported into an electronic database (EndNote 9.0).

Study Selection

Two reviewers independently assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above. Disagreements were resolved using a consensus process. Full-text articles of potentially relevant abstracts were retrieved and a second review for inclusion was conducted by reapplying the inclusion criteria.

Data Abstraction

The following data were abstracted from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results when reported. In cases where only per-protocol results were reported, we calculated intention-to-treat results if the data for these calculations were available. In trials with crossover, outcomes for the first intervention were recorded if available. This was because of the potential for differential withdrawal prior to crossover biasing subsequent results and the possibility of either a "carryover effect" (from the first treatment) in studies without a washout period, or "rebound" effect from withdrawal of the first intervention.

Data abstracted from observational studies included design, eligibility criteria duration, interventions, concomitant medication, assessment techniques, age, gender, ethnicity, number of patients screened, eligible, enrolled, withdrawn, or lost to follow-up, number analyzed, and results.

Quality Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.[10, 11] We considered the following factors when rating internal validity: methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and

contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated "poor-quality"; trials that met all criteria were rated "good-quality"; the remainder were rated "fair-quality." As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet *combinations* of items of the quality assessment checklist. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the role of the funding source.

Appendix B also shows the criteria we used to rate observational studies. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good-quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair-quality if they met 3 to 5 criteria and poor-quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality based on pre-defined criteria (see Appendix B), based on a clear statement of the questions(s), inclusion criteria, adequacy of search strategy, validity assessment and adequacy of detail provided for included studies, and appropriateness of the methods of synthesis. Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. A particular randomized trial might receive 2 different ratings: one for effectiveness and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Evidence Synthesis

Effectiveness compared with efficacy. When available, we highlight *effectiveness* studies conducted in primary care or office-based settings that use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most *efficacy* studies. The results of effectiveness studies are more applicable to the "typical" patient than results from highly selected populations in efficacy studies. Examples of "effectiveness" outcomes include quality of life, global measures of academic success, and the ability to work or function in social activities. These outcomes are more important to patients, family and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy studies provide the best information about how a drug performs in controlled settings that allow for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most, patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria, which may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have "comorbid" diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that, in practice, are used for much longer periods of time. Finally, they tend to use

objective measures of effect that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Data presentation. We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Studies that evaluated 1 nasal corticosteroid against another provided direct evidence of comparative benefits and harms. Outcomes of changes in symptom measured using scales or tools with good validity and reliability are preferred over scales or tools with low validity/reliability or no reports of validity/reliability testing. Where possible, head-to-head data are the primary focus of the synthesis. No meta-analyses were conducted in this review due to heterogeneity in treatment regimens, use of concomitant medications, outcome reporting and patient populations.

In theory, trials that compare these drugs to other interventions or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Indirect data are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

When analyses of statistical significance were not presented, Fisher's exact test was performed using StatsDirect (CamCode, U.K.) when adequate data were provided.

RESULTS

Overall results of literature search

We identified 1,404 (Update 1: 282) articles from literature searches and reviews of reference lists. This includes citations from dossiers submitted by the manufacturers of mometasone, fluticasone, and budesonide (Update 1: budesonide aqueous, fluticasone furoate, mometasone furoate, and triamcinolone acetonide.) After applying the eligibility and exclusion criteria to the titles and abstracts, we obtained copies of 489 (Update 1: 77) full-text articles. After re-applying the criteria for inclusion, we ultimately included 84 (Update 1: 29) publications, including 9 from submitted dossiers. The results of our literature search are detailed in Appendix C.

Overall summary of the evidence

Effectiveness

- No effectiveness trials were identified

Efficacy and adverse effects

Adults

Seasonal allergic rhinitis in adults:

- There were no significant differences between nasal corticosteroids in their effects on rhinitis symptoms overall in head-to-head trials. On average, 78% to 88% of adults with seasonal allergic rhinitis in head-to-head trials were rated by physicians as demonstrating significant global improvement.

- Based on evidence from placebo-controlled trials, both ciclesonide and fluticasone furoate were significantly better than placebo in improving seasonal allergic rhinitis symptoms and quality of life scores. Where reported, changes in RQLQ scores were similar to those in head-to-head trials of other nasal corticosteroids.

Perennial allergic rhinitis in adults:

- Very few differences in efficacy were reported in head-to-head trials involving beclomethasone, budesonide, fluticasone, or mometasone in adults with perennial allergic rhinitis.
    - Budesonide aqueous 256 mcg was associated with a significantly greater mean point reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 compared with -1.65, P=0.031) in one 6-week trial of 273 patients.[12]
    - It is unknown how new form of flunisolide or triamcinolone compare to other nasal corticosteroids due to a lack of head-to-head trial evidence.

- Quality of life outcomes were rarely reported in head-to-head trials and beclomethasone, fluticasone, and triamcinolone were associated with similar levels of improvement.

- Results from placebo-controlled trials of ciclesonide found improved quality of life scores relative to placebo. The effect of fluticasone furoate on quality of life outcomes is unclear; results from 2 unpublished studies are mixed.

- No head-to-head trials of adults with non-allergic rhinitis were identified. No indirect comparisons were made across placebo-controlled trials of fluticasone and mometasone due to heterogeneous efficacy outcome reporting.

- There were generally no significant differences between nasal corticosteroids in rates of withdrawals due to adverse events, headache, throat soreness, epistaxis, and nasal irritation when used in adults with seasonal or perennial allergic rhinitis in head-to-head trials that compared similar dose levels.

    - The old form of flunisolide was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ and the newer form of flunisolide across 2 head-to-head trials of adults with perennial allergic rhinitis.

- Cataract development was only reported in 1 observational study and there were no significant differences in incidence rates associated with beclomethasone use compared to nonuse.

- No evidence of glaucoma-associated adverse events was identified.

- Mometasone *prophylaxis* was superior to beclomethasone *prophylaxis* in preventing rhinitis symptoms during pre- and peak-seasons, but mometasone *prophylaxis* was also associated with significantly higher rates of headache.

Children

- In children, head-to-head trials of seasonal and perennial allergic rhinitis are few and beclomethasone, fluticasone, and mometasone were associated with similar reductions in rhinitis symptoms and with similar rates of more common respiratory and nervous system adverse effects. Evidence from placebo-controlled trials was insufficient for further assessment of comparative effects.

- No trials of children with non-allergic rhinitis were identified.

- Growth retardation in children:

    - Beclomethasone was associated with significantly lower height increase over 12 months relative to placebo in 1 trial and was similar to expected height increases over 3 years in a retrospective observational study**.**
    - In placebo-controlled trials, neither fluticasone, mometasone, nor budesonide were associated with growth retardation after 12 months.

- Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported.

Subgroups

- Evidence is insufficient to draw any conclusions about comparative effectiveness, efficacy, or safety in subgroups based on demographics, concomitant use of other medications, comorbidities (e.g., asthma, daytime somnolence/sleep disturbances), or pregnancy.

Detailed assessment

Key Question 1. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in effectiveness?

Seasonal Allergic Rhinitis

I. Adults with seasonal allergic rhinitis

A. Description of trials in adults with seasonal allergic rhinitis

We included 15 head-to-head trials of nasal corticosteroids for the treatment of seasonal allergic rhinitis in adults (Table 3, Evidence Tables 1 and 2).[13-27]

Table 3. Head-to-head trial comparisons in adults with seasonal allergic rhinitis

	Beclomethasone	Old flunisolide	New flunisolide	Triamcinolone	Fluticasone p.	Mometasone	Budesonide
Beclomethasone		**3**		**1**	**2**	**2**	**1**
Old flunisolide			**2**				
New flunisolide							
Triamcinolone					**3**[a]		
Fluticasone p.							**1**
Mometasone							
Budesonide							

[a] One trial used triamcinolone aerosol nasal spray propelled with CFC

The studies ranged from 2 to 8 weeks in duration and there were no open-label studies. Eight studies were single blind in design[13-15, 18-20, 23, 26, 27] and the rest were double-blind. One study had a cross-over design[24] and was designed primarily to examine the adverse effects between 2 medications and thus efficacy was only a secondary measure.[24] Another trial used a double-dummy design[28] that presents a unique issue for interpretation with this particular class of medications. The patients in this type of trial were exposed to the active drug and the placebo vehicle of the comparator. This creates some uncertainty for interpretation of the adverse events as sometimes it is the vehicle and not the active ingredient that is responsible for certain adverse effects.

Patients were characterized by an overall mean age of 34.1 years (range 24 years[21] to 66.7 years[20]) and 46.1% were female (range 8.5%[29] to 66.7%[20]). Only 40 percent of trials characterized trial populations by race and in those, the majority of patients were white (81.3-99%).[14, 19, 23, 25-27] Eligibility criteria differed across trials with regard to symptom severity, verification, and history and this is a potential source of heterogeneity across patient populations (Table 4). Trials also differed in which, if any, concomitant treatments were allowed and whether use of these was recorded.

Table 4. Seasonal allergic rhinitis trial characteristics

Trial	Eligibility criteria			Allowed concomitant treatments	
	Symptom severity scores	24-month history	Positive skin prick test	Antihistamines	Immunotherapy
Kaiser, 2004	TNSS ≥ 42	√	√		
Gross, 2002	TNSS ≥ 42	√	√		√
Ratner, 1992	INSS ≥ 200	√	√	√	
Graft, 1996[a]	TNSS ≤ 2	√	√		√
McArthur, 1994				√	
Langrick, 1984					√
Ratner, 1996	TSS = 2-7	√	√	√	√
Welsh, 1987		√	√	√	√
Stern, 1997		√	√	√	
Greenbaum, 1988		√	√	√	
Hebert, 1996	TSS ≥ 6; congestion ≥ 2 + one other symptom (INSS)	√	√	√	√
Lumry, 2003	RIS ≥ 24	√	√	√	√
Small, 1997	RIS ≥ 24	√	√		√
LaForce, 1994	INSS ≥ 200		√		√
Bronsky, 1987	EENT ≥ 8	√	√		

[a] Prophylaxis trial
TNSS=Total Nasal Symptom Score; INSS=Individual Nasal Symptom Score; TSS=Total Symptom Score; RIS=Rhinitis Index Score; EENT=Eye, Ear, Nose & Throat

No seasonal allergic rhinitis trial was rated good quality. All but 1 trial was rated fair quality.[24] The only trial rated poor, Greenbaum 1988, suffered from multiple flaws including inadequately described randomization and allocation concealment methods, a complete lack of inclusion criteria and reporting of baseline demographics, and excluded a number of patients from the outcome assessment.[24] The majority of the trials were sponsored by the pharmaceutical industry. Sponsor information was not reported in 1 trial[20] and 3 trials[24, 26, 29] did not acknowledge receiving funding but had authors employed by pharmaceutical companies.

No head-to-head trials in seasonal allergic rhinitis patients of the new drugs included in this update, ciclesonide and fluticasone furoate were identified through searches. One unpublished abstract of a head-to-head trial of fluticasone furoate 110 mcg/day compared with fluticasone 200 mcg/day provided by the manufacturer of fluticasone furoate suggested that fluticasone furoate was non-inferior to fluticasone in terms of efficacy and safety.[30] A published, peer reviewed report of these findings was not identified through literature searches, therefore these results should be considered inconclusive.

B. Results of trials of treatment in adults with seasonal allergic rhinitis

1. Direct comparisons

Similar proportions of patients experienced significant global improvements in rhinitis symptoms after 3 to 7 weeks of treatment based on physician assessment in head-to-head trials of nasal corticosteroids (Table 5). Physician assessment of global improvement was the most commonly reported outcome, was defined differently across trials, and was generally based on

patient diary ratings (0=none; 3=severe) of nasal symptom severity of rhinorrhea, stuffiness/congestion, nasal itching, and sneezing.

Three trials were associated with noticeably lower patient improvement rates.[16, 20, 26] The lowest rates of patient improvement were observed in a 7-week trial of flunisolide 200 mcg compared with beclomethasone 400 mcg (29% compared with 34%, NS).[20] Reasons for why the rates in this trial differed from the others may have been that the mean age was noticeably higher at 66.7 years and the outcome definition of "total improvement" appeared to be more stringent than in the other trials. Rates of patient improvement were also quite low in the only trial to prohibit concomitant usage of both antihistamines and immunotherapy.[26] The third lowest patient improvement rates came from the trial with the shortest treatment period of only 2 weeks. Patient improvement rates may have been lower in this trial because the treatments may not have reached their maximum effect within that time.[16]

Only 2 trials pre-specified a primary outcome measure, which was the mean change in composite rhinitis symptom score.[14, 15] Measurement of change in composite symptom scores was also the second most commonly reported outcome; however, these were defined differently across trials (Table 5). There were no significant differences between any 2 nasal corticosteroids in any of the trials that reported these outcomes for the treatment periods overall.[13-15, 17, 19, 21-23, 29]

There was a difference in 1 trial when primary outcome scores were analyzed only on days when the pollen count was greater than 10 grains/m^3.[14] Results of this trial demonstrated that budesonide 256 mcg per day was superior in reducing combined symptom scores, as well as the individual scores for sneezing and runny nose when compared to fluticasone 200 mcg and budesonide 128 mcg daily.[14]

Table 5. Rhinitis symptom assessment outcomes in adults with seasonal allergic rhinitis

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
McArthur, 1994 N=77 3 weeks	27 years 51%	Budesonide 200 mcg	Beclomethasone 200 mcg	Noticeably, very or total effective: 85% compared with 82%, NS	NR
Langrick, 1984 N=60 7 weeks	66.7 years 37.5%	Flunisolide 200 mcg	Beclomethasone 400 mcg	Total improvement: 29% compared with 34%, NS	NR
Welsh, 1987 N=100 6 weeks	28 years 33%	Flunisolide 200 mcg	Beclomethasone 336 mcg	Substantial (patient-rated): 80% compared with 75%, NS	Total hay fever score: +13.1% compared with +96.4%, NS
Bronsky, 1987 N=151 4 weeks	29 years 52%	Flunisolide 200 or 300 mcg	Beclomethasone 168 or 336 mcg	Major improvement: 27% compared with 38% compared with 40% compared with 46%, NS	NR
Ratner, 1992 N=136 2 weeks	44 years 62%	Fluticasone 200 mcg	Beclomethasone 336 mcg	Significant or moderate: 53% compared with 59%, NS	NR
Laforce, 1994 N=238 4 weeks	24 years 29%	Fluticasone 200 mg BID or QD	Beclomethasone 336 mcg	Significant or moderate: 65% compared with 70% compared with 65%, NS	TNSS: -43% compared with -53% compared with -32%, NS

Study Sample size Trial duration	Age % female	Treatment A	Treatment B	Physician-rated global evaluation of improvement (% pts)	% Change in total symptom score
Hebert, 1996 N=477 4 weeks	32 years 8.5%	Mometasone 100 or 200 mcg	Beclomethasone 400 mcg	Complete/marked relief: 77% compared with 79% compared with 74%, NS	TNSS: -53% compared with -59% compared with -59%; NS
Lumry, 2003 N=147 3 weeks	37 years 51%	Triamcinolone AQ 220 mcg	Beclomethasone 336 mcg	Greatly or somewhat improved: 78.4% compared with 87%, NS	Nasal Index: -42.9% compared with -45.9%, NS
Stern, 1997 N=635 4-6 weeks	Age NR 51%	Budesonide 128 or 256 mcg	Fluticasone 200 mcg	Substantial or total control - patients: 85% compared with 88% compared with 82%, NS	Combined nasal symptom score[a]: -26.5% compared with -29.4% compared with -29.4%, NS
Kaiser, 2004 N=295 3 weeks	31.6 years 62%	Triamcinolone AQ 220 mcg	Fluticasone 200 mcg	NR	TNSS: -48% compared with -49.7%, NS
Gross, 2002 N=352 3 weeks	38.8 years 66.5%	Triamcinolone AQ 220 mcg	Fluticasone 200 mcg	NR	TNSS: -49.4% compared with -52.7%, NS
Small, 1997 N=233 3 weeks	28 years 52%	Triamcinolone HFA 220 mcg	Fluticasone 200 mcg	NR	RIS**: -55% compared with -60%, NS
Ratner, 1996 N=218 6 weeks	44 years 62%	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	TNSS means: 3.81 compared with 3.55; NS
Greenbaum, 1988 N=122 4 weeks	NR NR	New flunisolide 200 mcg	Old flunisolide 200 mcg	NR	NR

[a] Prespecified as primary outcome

Three trials reported quality of life outcomes based on assessments using the 28-item Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ).[19, 23, 27] RQLQ items are organized into 7 dimensions (activities, emotions, eye symptoms, nasal symptoms, non-hay fever problems, practical problems, and sleep) and each are rated using a 7-point Likert Scale (0 to 6; lower scores indicate better QOL). Triamcinolone AQ 220 mcg was associated with similar mean reductions in RQLQ total score after 3 weeks relative to beclomethasone[19] and fluticasone (Table 6).[23, 27]

Table 6. Mean change in RQLQ total score

Study Sample size Trial duration	Age % female	Treatments	Point reductions
Lumry, 2003 N=147 3 weeks	37 years 51%	Triamcinolone AQ 220 mcg compared with beclomethasone 336 mcg	-1.71 compared with -1.79, NS
Berger, 2003 N=295 3 weeks	31.6 years 62%	Triamcinolone AQ 220 mcg compared with Fluticasone 200 mcg	-2.4 compared with -2.5, NS
Gross, 2002 N=352 3 weeks	38.8 years 66.5%	Triamcinolone AQ 220 mcg compared with Fluticasone 200 mcg	-2.4 compared with -2.5, NS

RQLQ=Rhinoconjunctivitis Quality of Life Questionnaire

Nine trials included an analysis of the mean percentage change in severity of eye symptoms.[13, 14, 17-20, 23, 25, 26] Out of those 9 trials, only 5 reported the raw data for comparison of numerical reduction in symptom severity and no differences between nasal corticosteroids were reported.[13, 14, 17, 19, 26] When the reduction in eye symptoms is compared to the reduction for other symptoms of seasonal allergic rhinitis in these head-to-head trials it tends to be less dramatic.

2. Indirect comparisons

As no published head-to-head trials were identified through searches, the evidence on the effectiveness of ciclesonide and fluticasone furoate in seasonal allergic rhinitis patients is limited to placebo-controlled trials.

Two trials comparing ciclesonide 200 µg/day to placebo had similar patient populations and primary outcomes (Table 7 and Evidence Table 1a).[31, 32] In both trials, ciclesonide 200 µg/day was associated with a significant improvement in morning and evening reflective TNSS relative to placebo. The sole trial that included other doses (25, 50, and 100 µg/day) of ciclesonide found it to be significantly more effective than placebo in improving TNSS only at the 100 µg/day dose.[31] Physician-rated evaluation of symptom improvement was reported qualitatively in 1 trial and quantitatively in the other; both found that ciclesonide appeared to be associated with some symptom improvement when compared to placebo. One trial included quality of life outcomes.[32] Patients taking ciclesonide experienced a mean change in RQLQ score of -1.17 at 4 weeks, which is similar to the change found in seasonal allergic rhinitis patients taking other nasal corticosteroids (shown in Table 6) but was not significantly different from placebo for this endpoint. However, at 2 weeks, RQLQ was significantly better with ciclesonide use relative to placebo (P=0.002). Ratner, et al. surmised this may have been due to reduced pollen counts during the time of the study rather than a true loss of effectiveness.[32]

An additional small, short-term (7 day) placebo-controlled crossover trial in 24 asymptomatic seasonal allergic rhinitis patients comparing the effect on nasal symptoms following intranasal administration of pollen extracts found that there was less immediate nasal irritation (itching, rhinorrhea) following ciclesonide use relative to placebo.[33]

Table 7. Efficacy outcomes in trials of ciclesonide compared with placebo

Study Sample size Duration	Mean age % female	Interventions	Change from baseline in total symptom score (TNSS)[a]	Physician-rated global evaluation of improvement	Change in RQLQ; point reductions
Ratner, 2006a N=726 2 weeks	40 years 71% female	Ciclesonide 25 µg/day - 200 µg/day compared with placebo	Ciclesonide 25 µg/day: -4.8 (sum baseline score: 18.72) Ciclesonide 50 µg/day: -4.8 (sum baseline score: 18.35 Ciclesonide 100 µg/day: -5.3 (sum baseline score: 18.71) *P*=0.04 compared with placebo Ciclesonide 200 µg/day: -5.8 (sum baseline score 18.82) *P*=0.003 compared with placebo Placebo: -4.2 (sum baseline score 17.80)	Reported as 'somewhat better' than placebo for 100 and 200 µg/day doses	NR
Ratner, 2006b N=327 4 weeks	40 years 75% female	Ciclesonide 200 µg/day compared with placebo	Ciclesonide 200 µg/day: -2.40 (mean baseline score 8.96) *P*<0.001 compared with placebo Placebo: -1.50 (mean baseline score 8.83)	Change in PANS: Ciclesonide 200 µg/day: -1.69 (SE 0.15) Placebo: -0.92 (SE 0.15); *P* <0.001	Ciclesonide 200 µg/day: -1.39; *P*=0.244 compared with placebo Placebo: -1.21

[a] The primary outcome in both trials was the mean change in reflective TNSS at day 14. Ratner 2006a used the *sum* of morning and evening scores as a baseline measurement, while Ratner 2006b used the *mean* of morning and evening scores as a baseline measurement.

Evidence regarding the efficacy of fluticasone furoate in seasonal allergic rhinitis patients comes from 3 well-designed placebo-controlled trials.[34-36] In the 3 trials, fluticasone furoate was significantly better than placebo at ameliorating the nasal and ocular symptoms associated with seasonal allergic rhinitis based on reflective TNSS and TOSS and in improving RQLQ scores (Evidence Table 1a; Table 8).

Table 8. Efficacy outcomes in trials of fluticasone furoate compared with placebo

Study Sample size Duration Mean age % female	Interventions	Change from baseline in total symptom score (TNSS)	Change from baseline in total ocular symptom score (TOSS)	Proportion of patients reporting improvement in overall response to therapy	Change (improvement) in RQLQ
Fokkens, 2007 N= 285 2 weeks 30 yrs 53% female	Fluticasone furoate 100 µg/day compared with placebo	Fluticasone furoate -4.94 compared with placebo -3.18 (mean difference -1.757; *P*<0.001)	Fluticasone furoate -3.00 compared with placebo -2.26 (mean difference -0.741 (CI -1.14 to -0.34; *P*<0.001)	Fluticasone furoate 67% compared with placebo 39% (*P*<0.001)	Fluticasone furoate -2.23 compared with placebo -1.53 (mean difference -0.700; *P*<0.001)
Kaiser, 2007 N= 299 2 weeks 35 yrs 60% female	Fluticasone furoate 100 µg/day compared with placebo	Fluticasone furoate -3.55 compared with placebo -2.07 (mean difference: -1.473 (CI -2.01 to -0.94; *P*<0.001)	Fluticasone furoate -2.23 compared with placebo -1.63 mean difference: -0.600 (CI -1.01 to -1.19; *P* =0.004)	Fluticasone furoate 73% compared with placebo 52% (*P*<0.01)	Reported as 'significantly higher' in fluticasone furoate patients (*P*<0.001)
Martin, 2007 N= 641 2 weeks 39 yrs 66% female	Fluticasone furoate 55-440 µg/day compared with placebo	Fluticasone furoate 55 µg -3.5 Fluticasone furoate 110 µg -3.84 Fluticasone furoate 220 µg -3.19 Fluticasone furoate 440 µg -4.02 placebo -1.83 *P*<0.001 compared with placebo for all doses	Fluticasone furoate 55 µg -1.93 Fluticasone furoate 110 µg -2.08 Fluticasone furoate 220 µg -1.92 Fluticasone furoate 440 µg -2.43 placebo -1.34 *P*<0.001 compared with placebo for all doses	Fluticasone furoate 55 µg 16% Fluticasone furoate 110 µg 28% Fluticasone furoate 220 µg 23% Fluticasone furoate 440 µg 26% placebo 8% *P*<0.001 compared with placebo for all doses	All fluticasone doses: range -1.79 to -1.97 placebo -0.97; *P*≤0.006

C. Results of prophylaxis trials in adults with seasonal allergic rhinitis

Mometasone was associated with significantly lower levels of rhinitis symptom severity in the peak- and pre-seasons relative to beclomethasone in the only head-to-head trial of seasonal allergic rhinitis prophylaxis. This double-blind, parallel-group trial was conducted throughout 9 centers in the United States for adult and adolescent patients ranging in age from 12 to 69 years of age.[25] The patients were required to be free of symptoms (nasal and non-nasal) at the baseline visit in order to be randomized to receive either beclomethasone 168 mcg twice daily or mometasone 200 mcg once daily plus placebo in the evening for 8 weeks. The patients in this trial starting taking the nasal corticosteroids, on average, 23 days before the onset of ragweed season and recorded the severity of their symptoms twice daily in a diary. A physician evaluated the severity of the patient's symptoms at screening, day 1 (baseline), and days 8, 22, 29, 36, 50, and 57. The patients in the mometasone and beclomethasone groups had comparable severity scores at baseline; however, the mometasone group had a lower mean nasal symptom score from baseline to the start of the season when compared to beclomethasone treated patients. This is significant because the patients started taking the medication before the start of pollen season, so the mometasone may have conferred some early benefit for patients. The authors concluded that the proportion of minimal symptom days (total nasal symptom score ≤ 2) were similar between treatment groups at all time points assessed.

II. Children with seasonal allergic rhinitis

A. Direct comparisons

Physician-rated total nasal symptom score reductions were similar for mometasone and beclomethasone after 4 weeks in the only head-to-head trial of children with seasonal allergic rhinitis (N=679) (Evidence Tables 1 and 2).[37] This fair quality, double-blind, parallel group, placebo-controlled, RCT conducted in pediatric patients, compared 3 doses of mometasone to beclomethasone.[37] This was a 4-week trial that took place in 20 centers throughout the United States. Patients ranged in age from 6 to 11 years old and were randomized to receive mometasone 25, 100, or 200 mcg daily, beclomethasone 84 mcg twice daily, or placebo. The mean reduction in physician-rated total nasal symptom score at day 8 did not demonstrate any difference between the 3 mometasone doses nor between mometasone and beclomethasone. However, between days 16 and 29, patients treated with mometasone 100 and 200 mcg daily improved, whereas those treated with mometasone 25 mcg demonstrated little further reduction of symptoms. By day 29, mometasone 100 and 200 mcg daily and beclomethasone were significantly more effective at reducing symptoms than mometasone 25 mcg daily. Thirty-three patients withdrew from the study, 14 patients (2%) due to adverse events.

B. Indirect comparisons

Placebo-controlled trials were evaluated for potential indirect comparisons to address the dearth of head-to-head evidence in children (Evidence Tables 3 and 4). Fluticasone 100 or 200 mcg,[38-42] triamcinolone 110 or 220 mcg,[43, 44] flunisolide 150 or 200 mcg,[45, 46] and beclomethasone 42 mcg[47] were all associated with significantly greater levels of symptom relief relative to placebo in 2- to 4-week, fair-quality trials in pediatric patients with seasonal allergic rhinitis (Table 9). Patients were mostly male and mean ages ranged from 8.3 to 10.5 years in all but 1 trial.[38] One trial of fluticasone involved 243 adolescents with a mean age of 14.2 years.[38] Eligibility for all trials required positive skin prick tests to a variety of allergens. Extreme heterogeneity in outcome reporting methods across trials precluded any quantitative analyses of indirect comparative efficacy.

No published trials of the new drugs included in this update, fluticasone furoate and ciclesonide were identified through literature searches; evidence on the efficacy of these drugs is available from two 2-week unpublished studies provided by the manufacturers of each drug.[48, 49] In both studies, there was a significant difference between the intervention group and placebo in reflective TNSS scores when the higher dose of each drug was used (110 mcg/day fluticasone furoate and 200 mcg/day ciclesonide) but not at the lower doses (55 mcg/day fluticasone furoate and 100 mcg/day ciclesonide.)

Table 9. Main results in placebo-controlled trials in children with seasonal allergic rhinitis

Study Sample size	NCS (total daily dose) x duration (weeks)	Main results
Kobayashi, 1989 N=101	Beclomethasone 168 mcg x 3	Significant decline in nasal obstruction, rhinorrhea, sneezing, and nasal itch as rated by physicians and patients (data NR)
Strem, 1978 N=48	Flunisolide 150 mcg x 4	All symptoms combined absent or questionably noted (# days): 5.6 compared with 1.2; *P*<0.0001 Patient felt spray achieved 'total control' (% pts): 16.7% compared with 4.2%; *P*=0.0011
Gale, 1980 N=35	Flunisolide 200 mcg x 4	Substantial or total control (% pts): 64% compared with 33%; *P*<0.05 Individual symptom relief: sneezing=NS; stuffy nose *P*<0.05; runny nose *P*<0.05; eye itch=NS
Boner, 1995 N=143	Fluticasone 100 or 200 mcg QD x 4	Percentage of symptom-free days: Sneezing=55% compared with 42% compared with 22%; *P*<0.05 Rhinorrhea=70% compared with 59% compared with 30%; *P*<0.05
Galant, 1994 N=249	Fluticasone 100 or 200 mcg QD x 4	'Significant improvement' (% pts; clinician-rated): 29% compared with 35% compared with 11%; *P*<0.01 'Magnitude' of improvement (% reduction in pt-rated mean total nasal symptom scores): 50-57% compared with 37%; *P*<0.05
Grossman, 1993 N=250	Fluticasone 100 or 200 mcg QD x 2	'Significant improvement' (% pts; clinician-rated): 29% compared with 21% compared with 9%; *P*<0.002
Munk, 1994 N=243	Fluticasone 100 or 200 mcg QD x 2	'Significant improvement' (% pts; clinician-rated): 33% compared with 32% compared with 9%; *P*<0.001
Schenkel, 1997 N=223	Triamcinolone 110 or 220 mcg x 2	Adjusted mean change from baseline in Nasal Index: -2.62 compared with -2.50 compared with -1.78; *P*<0.05
Banov, 1996 N=116	Triamcinolone 220 mcg QD x 2	Adjusted mean change from baseline in Nasal Index: -2.30 compared with -1.16; *P*<0.05

Perennial Allergic Rhinitis

I. Adults with perennial allergic rhinitis

A. Results of literature search

We identified 19 head-to-head trials that compared efficacy of 2 nasal corticosteroids for perennial allergic rhinitis (Evidence Tables 5 and 6).[12, 50-67] No good quality study was found. Eleven studies were rated fair quality[12, 50-59] and 8 studies were rated as poor.[60-67] Table 10 summarizes the combinations of comparisons.

Two recent systematic reviews were also identified through searches; both included studies with mixed AR populations. While these reviews focused largely on patient preference and cost, both also found little difference in effectiveness and safety among the nasal corticosteroids.[68, 69]

Table 10. Head-to-head trial comparisons

	Beclomethasone	New flunisolide	Old flunisolide	Triamcinolone	Fluticasone p.	Mometasone	Budesonide
Beclomethasone		**4**		**3**	**3**	**1**	**2**
New flunisolide			**1**				
Old flunisolide							
Triamcinolone							
Fluticasone p.						**1**	**2**
Mometasone							**2**
Budesonide							

B. Description of trials in adults with perennial allergic rhinitis

The studies for perennial and mixed allergic rhinitis were generally similar in design, inclusion/exclusion criteria, population, and duration, but did vary greatly in size. No good quality study was found. Eleven studies were rated fair quality[12, 38, 50-59] and 8 studies were rated as poor.[60-67] Poor quality ratings were due to the presence of combinations of multiple serious flaws including inadequate reporting of methods of randomization and allocation concealment, differences between group demographic and prognostic factors at baseline, and exclusion of patients from outcome assessments.[60-67]

All but 1[51] of the trials comparing beclomethasone to flunisolide were randomized. Six of these studies were double-blinded,[12, 52, 53, 56, 57, 59] 3 were open-label,[50, 51, 54] and 2 did not report blinding methods.[55, 58] Most of these trials were multicentered, while 4 were performed at a single center.[50, 51, 54, 55]

The populations studied were young to middle aged adults with mean ages mostly around 30-40 years and with balanced numbers of male/female subjects; 3 studies reported >60% females [51, 55, 59] and 1 reported <30% females.[54] Several trials did, however, include adolescents between 12-18 years.[52, 53, 55-57] All trials included patients with perennial rhinitis determined clinically or using various allergy tests and some also reported the proportion of participants with concomitant seasonal allergic rhinitis.[50, 56, 57] The studies varied widely in size from as few as 24 patients to as many as 548 patients. Most studies involved over 300 patients.[12, 52, 56-59] Duration of the trials ranged from 3 weeks to 1 year, with most around 4-8 weeks.

Most studies reported receiving financial or personnel support from pharmaceutical companies with the exception of 2 trials that did not report any source of external support.[54, 55]

Nine out of the ten studies measured efficacy outcomes using a 4-point scale to describe the severity of individual nasal and non-nasal symptoms with 0=none and 3=severe and 1 trial used a visual analog scale from 1-100 for 2 separate individual symptoms.[52] However, reporting methods for primary outcome measures varied widely among the trials, which prevents valuable indirect comparisons. These methods include reductions in points for individual symptoms and composite scores of individual symptoms, percent reduction of individual and/or composite scores and mean daily scores. The composite scores such as Nasal Index Score and Total Nasal Symptom Score include all or some of the measured individual symptoms. In addition, the trials reported physician assessments of symptoms, global evaluation of clinical efficacy and acceptability, onset of action, and amount of rescue medication required as secondary outcomes.

C. Results of trials of treatment in adults with perennial allergic rhinitis

1. Direct comparisons

The only evidence suggesting superiority of any 1 nasal corticosteroid over another comes from one 6-week trial of 273 patients with perennial allergic rhinitis in which budesonide aqueous 256 mcg was associated with a significantly greater mean reduction in a combined nasal symptom score relative to fluticasone aqueous 200 mcg (-2.11 compared with -1.65, P =0.031).[12] There were no significant differences between nasal corticosteroids in perennial allergic rhinitis symptom reductions when compared at *similar* dosages in most other trials (Tables 11 and 12).[52, 56-58]

Fluticasone aqueous 400 mcg/day appeared superior to relatively lower dosages of beclomethasone aqueous (400 mcg/day) in reducing individual symptoms (nasal discharge, nasal blockage, eye watering and irritation, nasal itching, sneezing) over the duration of a year in the longest of the head-to-head trials.[53] The disparity of dosage levels between treatments used in this trial raise questions about how to interpret this finding, however.

Table 11. Reductions in nasal symptom scores in head-to-head trials of perennial allergic rhinitis patients

	Beclomethasone AQ	Budesonide AQ	Mometasone AQ	Fluticasone p. AQ
Beclomethasone AQ		No evidence	No differences[56]	Mixed[52, 53]
Budesonide AQ			No differences[58]	**Budesonide superior**[12]
Mometasone AQ				No differences[57]
Fluticasone p. AQ				

It is unknown how the new[51] or old[50] forms of flunisolide 200 mcg compare directly to the new aqueous form of beclomethasone because both have only been compared to the discontinued aerosol form of beclomethasone 400 mcg in 4-week trials. No other head-to-head trials comparing either form of flunisolide directly to any other nasal corticosteroid in perennial allergic rhinitis patients were identified. The new and old forms of flunisolide were compared directly to each other in one 4-week trial and both were associated with similar reductions in individual symptom scores (sniffing, stuffiness, sneezing, postnasal drainage).[59] No fair- to good-quality trial of the *direct* comparative efficacy of triamcinolone relative to other nasal corticosteroids was identified.

Beclomethasone compared with fluticasone

Mixed findings were reported across 2 head-to-head trials comparing efficacy of beclomethasone to fluticasone (Table 10).[52, 53] While 1 study comparing standard doses of the 2 drugs found no significant differences in total symptom score,[52] the other trial found that an above maximum daily dosage of fluticasone propionate (400 mcg) was superior to a maximum dosage of beclomethasone (400 mcg) in reducing most individual symptoms.[53]

The British multicenter trial compared non-equivalent doses of the drugs (beclomethasone 200 mcg to fluticasone 200 mcg, both twice daily) for up to 1 year in 242 patients.[53] The population included adolescents aged 16 and over and adults with perennial

rhinitis based on clinical history, not an allergy test. There was no composite symptom score reported but only individual symptom scores for nasal and non-nasal symptoms. Results showed that fluticasone had significantly better symptom grades for nasal discharge, nasal blockage, and eye watering and irritation than beclomethasone.

The other study compared fluticasone 100 mcg either once or twice daily to beclomethasone 168 mcg or placebo twice daily in 466 adults and adolescents as young as 12 years for 6 months.[52] The outcome measures were expressed as reduction of total symptom scores using a visual analog scale (0-100 for each of 4 nasal symptoms). The study found no significant differences in efficacy between any of active drugs, both of which showed at least 45% reduction in total symptom score. It was noted that equivalent dosages of beclomethasone (400 mcg) and fluticasone (200 mcg) also had similar efficacy and safety in an unpublished 4-week randomized double-blind placebo-controlled parallel group trial of 286 adult patients with perennial rhinitis that was identified in the dossier provided by the manufacturer of fluticasone.[70] Drop-out rates for beclomethasone, fluticasone 100 and 200 mcg, and placebo (28% compared with 23% compared with 14% compared with 28%) in the published trial were noted to be relatively higher than in other similar trials.

Mometasone

Mometasone was associated with generally similar reductions in rhinitis symptoms relative to beclomethasone[56] and fluticasone[57] across 2 head-to-head trials (Table 10). One double-blind RCT compared beclomethasone 400 mcg twice daily to mometasone 200 mcg once daily in 427 adults and adolescents as young as age 12 with perennial allergic rhinitis.[56] The study population included 45-54% patients with seasonal allergies and 18-24% with concomitant asthma. The primary outcome in this 12-week study was measured with mean percent reduction in total morning and evening symptom scores within the first 15 days.

A trial comparing fluticasone to mometasone revealed mixed results for differences in efficacy.[57] One double-blind multicenter RCT compared fluticasone 200 mcg to mometasone 200 mcg in 550 adults and adolescents as young as 12 years with confirmed perennial allergic rhinitis. This fair-quality 12-week study included 37.5% patients with concomitant seasonal allergies. The primary outcome of mean percent reduction in total nasal symptom score had to be estimated from figures provided in the article. Although mometasone resulted in greater reduction of the total nasal symptom score, this patient-rated outcome was not significantly different between the 2 drugs. There was, however, a significantly greater reduction in the same physician-rated secondary outcomes of nasal congestion, nasal discharge, and overall condition with mometasone.

Budesonide

One trial found budesonide to be more efficacious in treating combined nasal symptoms than fluticasone (Table 10).[12] This 6-week Canadian/Spanish study investigated budesonide 256 mcg compared with fluticasone 200 mcg compared with placebo in 273 adults with confirmed perennial allergic rhinitis.[12] There was a significantly greater reduction in combined nasal symptoms scores with budesonide (-2.11 compared with –1.65, P=0.031). Moreover, they found that budesonide was significantly better than placebo at reducing nasal blockage than was fluticasone, while improvement in all other individual symptom scores was similar for both drugs. The onset of action, measured in hours before significant step-score reductions, was

quicker for budesonide than fluticasone (36 h compared with 60 h). The secondary outcome of percentage of patients who reported substantial or total symptom control did not differ significantly between the 2 drugs.

The only head-to-head study investigating budesonide and mometasone for perennial rhinitis found the 2 drugs comparable for nasal symptom scores and overall symptom control. One fair-quality European RCT compared budesonide 256 mcg or 128 mcg to mometasone 200 mcg or placebo in 438 adults with confirmed perennial allergic rhinitis.[58] The primary efficacy outcome, nasal symptom score (morning and evening combined), was not significantly different in the 2 medications. Furthermore, there was no statistically significant difference for the secondary outcomes: percentage of patients experiencing no symptom control, consumption of rescue medication, and onset of action. We have identified unpublished quality of life data from this study in the dossier supplied by the manufacturer of budesonide that found no significant differences between treatments except that budesonide is superior to placebo for general health and vitality.

Flunisolide: New compared with old formulations

The randomized double-blind parallel-group study compared 2 different formulations of flunisolide aqueous in 215 patients with confirmed perennial allergic rhinitis and found similar efficacy in both treatments.[59] Dosages were equivalent in both the old and new formulations, which reduced propylene glycol from 20% to 5%, increased polyethylene glycol from 15% to 20%, and added 2.5% polysorbate in an effort to reduce nasal stinging and burning. There were no significant differences in mean reduction of total symptom and individual symptom scores between formulations. Further, patients rated acceptability of nasal burning/stinging on a 100-point visual analog scale. The original formulation had a mean score of 52 while the new formulation was rated as 87 ($P<0.001$).

Table 12. Outcomes in head-to-head trials of perennial allergic rhinitis patients

Study Sample size	Interventions (Total Daily Dose) Duration	Outcome	Results
Sahay, 1980 N=60	Flunisolide aerosol BID (200 mcg) **Beclomethasone aerosol** QID (400 mcg) 4 weeks	Reduction in mean symptom scores: (A) Sneezing (B) Stuffiness (C) Runny nose (D) Nose blowing (E) Post-nasal drip (F) Epistaxis	(A) -1.44 vs. -1.57 (B) -1.74 vs. 1.62 (C) -1.33 vs. 1.48 (D) -1.70 vs. -1.72 (E) -0.74 vs. -0.68 (F) -0.15 vs. -0.07 NS for all
Bunnag, 1984 N=45	Flunisolide BID (200 mcg) **Beclomethasone aerosol** QID (400 mcg) 4 weeks, then crossover	Overall symptom score	-2.91 compared with -4.96; $P<0.0005$
van As, 1993 N=466	Fluticasone p. aqueous BID (100 mcg) Fluticasone p. aqueous QD (200 mcg) **Beclomethasone aqueous** BID (168 mcg) 6 months	Reduction in Total Symptom Score (0-200)	≥ 45% for all (data NR), NS

Study Sample size	Interventions (Total Daily Dose) Duration	Outcome	Results
Haye, 1993 N=242	Fluticasone p. aqueous BID (200 mcg) **Beclomethasone aqueous** BID (200 mcg) ≤ 1 year	No overall score; only: (A) Nasal Discharge (B) Nasal Blockage (C) Eye watering and irritation (D) Nasal itching (E) Sneezing	Fluticasone > beclomethasone (data NR) (A) *P*=0.002 (B) *P*=0.002 (C) *P*=0.048 (D) *P*=0.052 (E) *P*=0.114
Al-Mohaimeid, 1993 N=120	Budesonide BID (400 mcg) **Beclomethasone** BID (400 mcg) 3 weeks	**(A) Mean daily symptom scores (blocked nose, runny nose, itchy nose, sneezing, runny eyes, sore eyes)** (B) % patients symptom free	(A) no differences for all but sneezing: 0.48 compared with 0.72, *P*=0.05 (B) 35% compared with 26%; NS
Day, 1998 N=273	Budesonide aqueous QD (256 mcg) Fluticasone p. aqueous QD (200 mg) 6 weeks	Reduction in combined nasal symptom scores	-2.11 compared with --1.65; *P*=0.031
Drouin, 1996 N=427	Mometasone aqueous QD (200 mcg) **Beclomethasone aqueous** BID (400 mcg) 12 weeks	Mean change in total AM + PM symptom diary scores over 15 days (estimated from figure)	46% compared with 51%, NS
Mandl, 1997 N=550	Mometasone aqueous QD (200 mcg) Fluticasone p. aqueous QD (200 mcg) 3 months	Mean change in total AM + PM symptom diary scores over 15 days (estimated from figure)	61% compared with 55%, NS
Bende, 2002 N=438	Mometasone aqueous QD (200 mg) Budesonide QD (256 mcg) Budesonide QD (128 mcg) 4 weeks	Reduction in Nasal Index Score (morning/evening)	-1.26/-1.44 compared with -1.45/-1.59 compared with -1.41/-1.50; NS
Meltzer, 1990 N=215	Flunisolide aqueous original formulation BID (200 mcg) Flunisolide aqueous new formulation BID (200 mcg) 4 weeks	Mean Reduction of Total Symptom Score, estimated from figure	-3.0 compared with -2.5, NS

Triamcinolone

Evidence was insufficient for analyzing the comparative efficacy of triamcinolone relative to any other nasal corticosteroids. The only head-to-head evidence identified for triamcinolone (220 mcg) comes from an open-label randomized parallel group 3-week trial of 175 perennial allergic rhinitis patients in which there were no differences in efficacy or safety endpoints when compared to fluticasone 200 mcg once daily.[70]

2. Indirect comparisons

Placebo-controlled trials of triamcinolone were evaluated due to the dearth of head-to-head evidence available for this nasal corticosteroid. There were 4 large (N=178 to 305) fair

quality placebo-controlled trials that assessed triamcinolone in patients with perennial allergic rhinitis and 1 very small study of cat allergic patients (N=12).[71-75] All of the larger studies reported significantly lower nasal symptoms for the active drug in treatment of perennial rhinitis. Storms, et al. investigated 3 different doses of triamcinolone aerosol (110 mcg, 220 mcg, and 440 mcg/day) compared with placebo in 305 patients and found nasal index (composite of 4 symptoms on 4-point scale, maximum 12 points) values after 12 weeks (weekly mean change from baseline) of -2.9, -3.5, -3.35 and -2.2 respectively, $P<0.05$.[71] Another study of 296 patients with mixed allergic rhinitis reported -4.80 compared with -3.55 ($P<0.001$), a significant reduction of mean score of daily total symptom score (maximum score 20 points, 5 symptoms on a 5-point scale) for triamcinolone aqueous 220 mcg and placebo respectively.[72] Potter, et al. also reported significant improvements in a Rhinoconjunctivitis Quality of Life Questionnaire in the areas of sleep, nasal symptoms, emotional problems, and overall quality of life compared to placebo.[72] The 12-week placebo-controlled trial of 205 perennial rhinitis subjects taking triamcinolone aerosol 200 mcg reported change from baseline nasal index (maximum 9 points) -3.16 compared with -2.36, $P<0.05$ for active drug and placebo, respectively.[74] A 4-week placebo-controlled trial of triamcinolone aqueous 220 mcg in 178 patients with perennial allergic rhinitis showed a significant overall reduction in nasal index (sum of 3 individual symptom scores, 4-point scale, 0=none and 3=severe) for triamcinolone compared with placebo, -2.07 compared with 1.27, $P<0.02$.[75] The 1-week crossover trial of triamcinolone 220 mcg followed by a 1-hour cat allergen challenge resulted in mean nasal symptoms (4-point scale, 0=none and 3=severe) of 0.65 compared with 1.0, $P=0.06$ for active drug and placebo, respectively.[73]

The effect of ciclesonide use in perennial allergic rhinitis patients was evaluated in 2 placebo-controlled trials (see Evidence Tables 5a and 6a.)[76, 77] Although inclusion criteria of these trials allowed enrollment of patients >12 years of age, the mean age was ~35 years in both trials. Other patient demographic characteristics were similar. Only 1 of the trials was designed to evaluate efficacy.[76] In that trial, patient-rated nasal symptoms (TNSS) and quality of life (RQLQ) were both significantly improved after 6 weeks of use in the ciclesonide group compared to the placebo group. There was a slight between-group difference in physician-rated symptoms favoring ciclesonide, although this difference did not reach statistical significance. In the longer trial (52 weeks) designed to evaluate safety outcomes rTNSS scores were significantly improved from baseline compared to placebo. There was also a statistically significant difference in RQLQ scores, favoring ciclesonide, at the study's endpoint. This difference was only clinically significant in the subset of patients who were more impaired at baseline (RQLQ scores ≥3.5).[77]

No published effectiveness or efficacy trials of fluticasone furoate were identified. The only evidence on the efficacy of fluticasone furoate in perennial allergic rhinitis patients comes from the dossier provided by the drug's manufacturer, which includes reference to 2 unpublished studies (duration of 4 and 6 weeks) evaluating symptom relief and quality of life outcomes. Compared to placebo, those patients receiving fluticasone furoate had a significant improvement in reflective TNSS in both studies. Significant improvement in ocular symptoms was not observed in the 4-week study[78] although a statistically significant improvement was observed in the 6-week study.[79] Similarly, RQLQ was significantly improved in 1 study (mean between group difference -0.65 [CI -0.90 to -0.40; $P<0.001$]). The manufacturer also identifies this as a clinically significant improvement.[78] The other trial failed to show an either statistically or clinically significant difference in RQLQ.[79]

II. Adolescents and children with perennial allergic rhinitis

A. Direct comparisons

Beclomethasone compared with fluticasone

The only head-to-head evidence in children and adolescents with perennial allergic rhinitis comes from a meta-analysis of combined data from a smaller (N=120) 12-week head-to-head trial comparing fluticasone 100 mcg once or twice daily with beclomethasone 200 mcg twice daily and a larger (N=415) 4-week placebo-controlled trial, which compared fluticasone 100 mcg or 200 mcg once daily with placebo.[80] There is no specific data reported for the comparator study, only the statement that fluticasone was as effective as beclomethasone in increasing the median percent of symptom-free days for all symptoms.

B. Indirect comparisons: Placebo-controlled trials

Since there was only 1 head-to-head comparison study involving children or adolescents that met review criteria, we looked at the available evidence from 10 placebo-controlled trials (Evidence Tables 7 and 8; Table 13).[81-90] Due to the heterogeneity of this evidence, no indirect comparisons of efficacy in children were possible.

A recent Cochrane review of placebo-controlled trials that included 3 older studies (Hill, Neuman, and Sarsfield; see Table 13 below) concluded that beclomethasone and flunisolide were likely more effective than placebo based on the very limited evidence available.[91]

No trials in children of the 2 new drugs included in this update (ciclesonide and fluticasone furoate) were identified. One published abstract of a 12-week placebo-controlled trial of fluticasone furoate in children aged 2 to 11 years was identified through the dossier provided by the drug's manufacturer. The limited results presented suggest that the 55µg dose is significantly better than placebo at reducing the nasal symptoms associated with perennial allergic rhinitis based on reflective TNSS.[92]

Table 13. Placebo-controlled trials in children/adolescents with perennial allergic rhinitis

Study Sample size	Interventions (Total daily dose) Duration	Mean age Age range % female	Outcome	Results
Day, 1990 N=51	Budesonide BID (200 mcg) Placebo 4 weeks	13.4 compared with 13.3 years, 7-18 compared with 6-18 years 53.4% compared with 40%	Difference in combined nasal symptom scores, including sneezing, blocked nose, itchy nose, runny nose	-0.95 ± 1.87 compared with -0.37 ± 1.38 P < 0.05
Fokkens, 2002 N=202	Budesonide aqueous QD (128 mcg) Placebo 6 weeks	10.5 compared with 10.7 years, 6-16 years, 34.3%	Difference in combined nasal symptom scores (evening), including sneezing, blocked nose, runny nose	-1.86 compared with -0.93; *P*<0.001

Study Sample size	Interventions (Total daily dose) Duration	Mean age Age range % female	Outcome	Results
Hill, 1978 N=22	Beclomethasone aerosol QD (300 mcg) Placebo 6 weeks then crossover	NR, 7-17 years, 50%	% children with improved nasal symptoms (lower mean daily diary score)	86.4% *P*<0.01 placebo results not reported
Shore, 1977 N=46	Beclomethasone aerosol (300 mcg) Placebo 3 weeks then crossover, followed by 3 months open label with active drug (200 mcg)	8 years, 4-12 years, 21.7%	Patient assessment that drug was effective	75% placebo results not reported
Neuman, 1978 N=30	Beclomethasone aerosol 4 times daily (200 mcg) Placebo 3 weeks then crossover	13.8 years, 9-18 years, 53.3%	Difference (baseline to end of study) in average daily symptom score on 4-point scale	Group I -2.5 compared with 0 Group II -2.5 compared with +2.65 (no washout period)
Ngamphaiboon, 1997 N=106	Fluticasone p. aqueous QD (100 mcg) Placebo 4 weeks	8.96 compared with 9.06 years, 5-11 years, 18.9% compared with 10.3%	Physician-rated mean total symptom score (sum of obstruction, rhinorrhea, sneezing and itching, scale 0-3)	-6.13 compared with -5.7, *P*<0.05
Todd, 1983 N=64	Flunisolide aqueous QD (150 mcg) Placebo 4 weeks then crossover	8.3 years, 3-17 years, 39%	Mean daily total symptom score (stuffy nose, sneezing, runny nose, nose blowing, and eye symptoms)	Significantly lower than placebo for Group II only for 11 of 28 days
Sarsfield, 1979 N=27	Flunisolide aqueous QD (150 mcg) Placebo 2 months then crossover	12.3 years, 7-16 years, 22%	Mean weekly symptom scores on 4-point scale (A) sneezing (B) stuffy nose (C) runny nose (D) nose-blowing	Week 4 (A) 0.64 vs. 1.17 (B) 1.04 vs. 1.00 (C) 0.62 vs. 0.85 (D) 1.10 vs. 1.45
Welch, 1991 N=210	Triamcinolone aerosol (165 mcg) Triamcinolone aerosol (82.5 mcg) Placebo 12 weeks	9 years, 4-12 years, 33%	Adjusted mean change from baseline total nasal symptom score in first 6 weeks (no escape medication allowed) and second 6 weeks (escape medication allowed)	Estimated from figure: first 6 weeks 2.65 compared with 2.2 compared with 1.65 second 6 weeks 3.35 compared with 2.75 compared with 2.05 *P*<0.01 for highest dose compared to placebo
Storms, 1996 N=137	Triamcinolone aerosol (220 mcg) Placebo 4 weeks	8.9 years, 6-11 years, 27% compared with 44%	Adjusted mean change from baseline nasal index: sum of symptom scores for nasal stuffiness, nasal discharge, and sneezing each on a 4-point scale	-2.27 compared with -1.36, *P*<0.05
Nayak, 1998 N=80	Triamcinolone aqueous (220 mcg) Triamcinolone aqueous (440 mcg) Placebo 6 weeks	9.5 years, 6-12 years, 37.5%	Outcome not eligible, for adverse events only	

Perennial Non-Allergic Rhinitis

I. Adults

A. Direct comparisons

There were no head-to-head efficacy trials that compared any nasal corticosteroids in adults with perennial non-allergic rhinitis that met the inclusion criteria of this review.

B. Indirect comparisons in placebo-controlled trials

We found 2 placebo-controlled studies of patients with non-allergic rhinitis that were not indirectly comparable due to heterogeneous efficacy outcome reporting (Evidence Tables 9 and 10). The first study of fluticasone reported efficacy for use in non-allergic rhinitis and the second study of mometasone revealed mixed results in this population.[93, 94]

A pooled analysis from 3 randomized, double-blind, double-dummy, placebo-controlled trials examining fluticasone aqueous 200 mcg and 400 mcg compared with placebo in 983 patients with non-allergic rhinitis (NARES) and without eosinophilia (non-NARES) reported clinical improvement of symptoms in the total population.[93] Both doses of active drug showed significant improvement in total nasal symptom score (100-point visual analog scale for individual symptoms, maximum possible 300) after 4 weeks compared to placebo, -84, -85, and -64 for the lower dose, higher dose, and placebo respectively, $P<0.002$. Differences for the individual subgroups, non-NARES and NARES, also favored active drugs, but did not report significance.

The fair quality multicenter, randomized, double-blind, placebo-controlled trial investigating mometasone 200 mcg found mixed results for the efficacy in 329 adult patients with non-allergic rhinitis.[94] The patient-rated improvement was numerically greater for mometasone than placebo, 56% compared with 49%; however this difference was not significant. The secondary efficacy variable of investigator-rated improvement was significantly greater for mometasone compared to placebo, 60% compared with 48% ($P=0.03$). Efficacy was reported as improvement rate, which was defined as reduction of at least 1 point in overall symptom score, comprising 4 individual symptoms on a 4-point scale for a maximum total of 12 points. The study also reported no significant difference in quality of life, but did not report methods or specific results.

Based on the results of 2 unpublished studies provided by the drug's manufacturer, fluticasone furoate was not significantly better than placebo at improving daily reflective TNSS in patients with non-allergic rhinitis triggered by changes in weather or temperature.[95, 96] Likewise, there was no significant difference in response to therapy between fluticasone furoate and placebo in either study. Full, published results of these studies were not identified through literature searches.

II. Children

No efficacy trials of nasal corticosteroids in children with perennial non-allergic rhinitis were identified.

Key Question 2. For adults and children with seasonal or perennial (allergic and non-allergic) rhinitis, do nasal corticosteroids differ in safety or adverse events?

All Rhinitis Types

I. Adults

A. Direct comparisons

Head-to-head trials served as the primary source of evidence for comparisons between nasal corticosteroids in incidence and severity of the more common adverse effects associated with shorter-term usage. No head-to-head trial was of sufficient duration to measure comparative risk of cataract development or worsening of glaucoma. Rates of withdrawals due to adverse events, headache, throat soreness, epistaxis, and nasal irritation were generally similar between nasal corticosteroids in head-to-head trials of adults/adolescents with either seasonal or perennial rhinitis (Appendix E).[12-21, 23-27, 29, 50-54, 56-59, 94, 97-100] One exception is that the old formulation of flunisolide 200 or 300 mcg was associated with significantly higher rates of nasal burning/stinging than beclomethasone AQ 168 or 336 mcg (30% compared with 33% compared with 10% compared with 10%; $P<0.05$)[26] and higher rates than the new formulation of flunisolide 200 mcg (13% compared with 0; $P<0.001$)[24] in 4-week trials of adults with seasonal allergic rhinitis. It is not yet clear how the new formulation of flunisolide 200 mcg ranks relative to other nasal corticosteroids with regard to nasal irritation effects. To-date, nasal burning/stinging rates associated with the new formulation of flunisolide have only been directly compared to the discontinued form of beclomethasone (20% compared with 2.2%; $P=0.0081$) in adults with perennial allergic rhinitis.[51]

The few other differences pertain to rates of headache and epistaxis. In the only trial of nasal corticosteroids used prophylactically, mometasone 200 mcg was associated with significantly higher rates of headache than beclomethasone 336 mcg in an 8-week trial of adults with seasonal allergic rhinitis (36% compared with 22%;; P = 0.02 calculated here using the Fisher's Exact Test using StatsDirect, CamCode, UK).[25] Additionally, fluticasone 200 mcg was associated with a significantly higher rate of epistaxis than a relatively lower dosage of beclomethasone 200 mcg (14% compared with 5%; $P=0.0285$) after a year or less in a trial of adults with perennial allergic rhinitis.[53] Fluticasone may have been at a disadvantage in this comparison due to the use of a relatively low dose of beclomethasone. This result was not consistent with 3 other trials using equivalent dosage comparisons.[16, 21, 52]

Six head-to-head trials assessed how adverse sensory attributes of nasal corticosteroids use (e.g., overall comfort, medication run-off, irritation, odor, taste) affected patient preferences (Evidence Tables 5 and 6).[101-106] These studies reported no consistent differences between treatments. One trial compared single doses of budesonide aqueous (64 mcg) with fluticasone (100 mcg or 200 mcg) and found differences only in sensory outcomes that were not relevant for this review.[103] No comparative adverse events data were reported. Another trial comparing single doses of triamcinolone aqueous, beclomethasone aqueous, and fluticasone aqueous in 94 adult patients with mixed allergic rhinitis showed no significant differences for nasal irritation, urge to sneeze, or drug run-off between treatment groups.[105] Meltzer, et al. compared single doses of

mometasone and fluticasone in 100 patients with allergic rhinitis and found no significant difference in nasal irritation or product run-off into throat or nose.[106]

The remaining 3 trials compared single doses of triamcinolone aqueous 220 mcg to fluticasone 200 mcg and mometasone 200 mcg[101, 102, 104] and only Stokes and Bachert revealed a significant difference in a relevant outcome. It should be noted that Stokes used a pooled analysis of 2 studies and Bachert reported more thoroughly the data from 1 of these studies. This fair to poor quality study found that triamcinolone aqueous had significantly less nasal irritation in the immediate and delayed (2-5 minute) measurements.[102] Bachert was the only study to report adverse events and found no significant difference between treatments.[104]

B. Indirect comparisons

Placebo-controlled trials and observational studies provided evidence of the risk of cataract development and longer-term adverse effects of nasal corticosteroids, including ciclesonide and fluticasone furoate. Evidence is extremely limited and insufficient for indirect comparisons between nasal corticosteroids.

1. Cataract

We identified 1 retrospective cohort study of cataract incidence in 88,301 patients younger than 70 years of age taking intranasal steroids in England and Wales (Evidence Tables 11 and 12).[107] Seventy percent of these patients used beclomethasone. The study compared nasal steroid users to a non-exposed population to determine the incidence rate/1000 person years and the relative risk of developing cataract as a result of treatment. Evidence showed that there was no increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2).

Ocular changes, including the development of cataracts, were infrequent in one 52-week placebo-controlled trial of ciclesonide, with no difference between the ciclesonide and placebo groups.[77]

We are aware of additional unpublished data from a comparative study of mometasone beclomethasone and placebo that found no clinically significant changes in results from ophthalmic exams during the 12-week study period. An unpublished 12-month open-label extension of the previously mentioned study reported no cataract and no significant differences in mean intraocular pressure between treatments groups.

2. Common adverse respiratory and nervous system effects of longer-term use

Triamcinolone

One open-label 12-month extension of a 4-week randomized placebo-controlled double-blind trial evaluated long-term safety and efficacy of triamcinolone aqueous (200 mcg with option to reduce to 100 mcg/day if symptoms are adequately controlled) in 172 patients with confirmed perennial rhinitis.[108] Adverse event rates potentially due to treatment were higher in the extension study than in the original controlled trial: Headache 22.1% compared with 6.8%, epistaxis 18 % compared with 6.8%, pharyngitis 32% compared with 14.8%, rhinitis 28.5 % compared with 6.8%, cough 8.1% compared with 0%, and sinusitis 15.7%. The authors note that

there is some overlap with the winter cold season and are not all clearly related to treatment with intranasal triamcinolone. The study also reports rates of adverse events related to topical effects possibly related to treatment that, although low, are higher in the long-term observation compared with the 4-week trial: nasal irritation 2.3% compared with 0%, naso sinus congestion 1.2% compared with 0%, throat discomfort and dry mucous membranes 0% in both studies, sneezing 0.6% compared with 0%, and epistaxis 12.8% compared with 4.5%.

Fluticasone propionate

A 12-month, randomized, double-blind, placebo-controlled parallel group trial of 42 patients with confirmed perennial allergic rhinitis treated with fluticasone aqueous 200 mcg/day reported only epistaxis as occurring more frequently in the active drug group.[109] There was 1 withdrawal due to an adverse event in the fluticasone group. Unpublished data from an open-label 52-week observational study of fluticasone 200 mcg twice daily in 60 patients with perennial rhinitis reported no serious or unexpected adverse events (http://www.fda.gov/cder/foi/nda/98/20121S009_Flonase.htm).

Fluticasone furoate

In a large (N=806) 12-month, placebo-controlled trial of fluticasone furoate most patients experienced an adverse event during time on trial (77% fluticasone furoate compared with 71% placebo). Patients treated with the active drug were more likely to experience epistaxis than those taking placebo (20% compared with 8%, respectively). While most of these were mild in the fluticasone furoate group, there were some moderate and severe episodes as well. All episodes of epistaxis in the placebo group were deemed mild. There was no difference between the 2 groups for other adverse event rates, including headache, cough, nasopharyngitis, and rhinitis.[110]

Ciclesonide

Evidence on the long-term safety on ciclesonide comes from 1 placebo-controlled trial of 663 patients. Mean duration of exposure to ciclesonide was 287.9 days. Rates of epistaxis were higher in the ciclesonide group (10% compared with 7.2% in the placebo group), as were rates of sinusitis and headache. Conversely, rates of nasopharyngitis and upper respiratory infection were higher in the placebo group. None of these differences were deemed to be clinically significant by the study's authors.[77]

Mometasone

A well-designed, open-label 4-week trial of mometasone 200 mcg in seasonal allergic rhinitis patients was consistent with the data from head-to-head trials in adverse event rates.[111]

II. Adolescents and children

A. Direct comparisons

Evidence of the comparative safety of nasal corticosteroids in adolescents and children is extremely limited and comes only from 3 head-to-head trials.[80, 112, 113] Richards and Milton concluded that there were no clear differences in treatment-related adverse events between fluticasone aqueous, beclomethasone, and placebo.[80] There were some numerical differences in epistaxis occurring most frequently with fluticasone 100 mcg, but they could not be found clinically significant due to relative rarity and varying severity of symptoms. There were also no differences found in rates of withdrawal due to adverse events between treatment groups. The next controlled trial compared mometasone to budesonide in 22 children aged 7-12 years with confirmed perennial, seasonal, or mixed allergic rhinitis.[112] There were no withdrawals due to adverse events and no clear differences in rates of adverse events between treatments or active drug and placebo. The study did not report individual adverse events separately for treatment groups. A randomized controlled double/single-blind trial examined 2 doses of triamcinolone and fluticasone in 49 children between 4-10 years old.[113] This trial studied short-term bone growth and effects of nasal steroids on the hypothalamic-pituitary-adrenal axis. These were not included in our adverse event review, but we were able to include the other clinical adverse events reported. There were no clear differences in all-cause adverse event rates among the treatment groups, triamcinolone 110 mcg (50%), triamcinolone 220 mcg (43.6%), fluticasone (43.6%), and placebo (49%). Fever was the only individual adverse event reported for all treatment groups and there were no clear differences among the groups for incidence of fever. There were 3 withdrawals due to adverse events in the triamcinolone 110 mcg group, 1 of which was treatment-related and 1 of which was due to adverse events in the placebo group.

B. Indirect comparisons

Due to the paucity of head-to-head trial evidence in adolescents/children, placebo-controlled trials were analyzed for further assessment of how nasal corticosteroids compare to one another, indirectly, in rates of more common adverse respiratory and nervous system effects and in effects on growth. The only evidence of the efficacy and safety of nasal corticosteroids in preschool-aged children also comes from a placebo-controlled trial.

1. Common adverse respiratory and nervous system effects

All eleven 2- to 12-week placebo-controlled trials reported miscellaneous tolerability outcomes such as nasal irritation, epistaxis/blood-tinged nasal secretions, headache, and others in children aged 8.3 to 12.3 years,[81, 82, 86-90, 114-117] and only 3 studies additionally reported effects on standing height.[114, 115, 117] The reporting of adverse effects in these trials was inconsistent across studies and thus, it is not possible to draw conclusive indirect comparisons. Day, et al. reported no significant difference in adverse effects between budesonide and placebo,[81] a 4-week study found no adverse events with fluticasone or placebo,[86] and the remaining 9 studies reported no clear differences in adverse effects between the active drug and placebo groups.[82, 87-90, 114-117]

The only evidence of safety in younger children between the ages of 2-5 years comes from a small (N=56) placebo-controlled trial of mometasone furoate. There were no serious adverse events found during the 6-week treatment period. Headache and rhinorrhea were more

common in the placebo group (7% mometasone furoate compared with 11% placebo for both AEs) while upper respiratory tract infection and skin trauma occurred in children using mometasone (7% for upper respiratory tract infection and 4% for skin trauma), although the latter adverse events were not reported in the placebo group.[118]

We identified 2 observational studies that included adolescent patients (12-18 yrs.). The first investigated open-label use of the new formulation of HFA propelled triamcinolone on 396 patients.[119] The smaller study evaluated mometasone furoate in 61 subjects.[120] Both studies found no serious adverse events related to treatment drugs and similar tolerability events as previously described.

2. Lenticular opacities

We identified 1 observational study that examined long-term safety of budesonide in 78 children with confirmed perennial rhinitis between the ages of 5-15 years.[121] There were 4 small lenticular opacities found; 2 were present before the study began and remained unchanged over 24 months of treatment and the other 2 were transient and disappeared upon discontinuation of budesonide treatment. There is no report of the clinical significance of these opacities.

3. Nasal carriage of staphylococcus aureus

We found 1 medium-sized fair quality observational study (N=196) of children (mean age 7.6 years) treated with fluticasone for allergic rhinitis for 2 months.[122] Baysoy, et al. found no significant difference in pre- and post-treatment staphylococcus aureus carriage rates between active treatment and control groups.

4. Growth retardation in children

The evidence of clinical growth effects comes from 4 randomized double-blind placebo-controlled trials and 2 observational studies.[114, 115, 117, 121, 123, 124] Changes were reported from baseline in statural growth, although the reporting methods varied somewhat among the studies. We excluded studies that only reported growth outcomes as measured using knemometry or hypothalamic-pituitary-adrenal (HPA) axis function. The use of short-term lower-leg growth rates measured with knemometry methods is less predictive of long-term growth due to the inconsistent and irregular timing of growth spurts in childhood.[115] Many studies of nasal corticosteroids have included the assessment of hypothalamic-pituitary-adrenal (HPA) axis function in order to determine the systemic effects, however the FDA has suggested that childhood growth may be a more sensitive indicator of these systemic adverse effects than the HPA axis function.[117]

Growth effects of beclomethasone AQ 168 mcg, fluticasone AQ 200 mcg, and mometasone 100 mcg were each compared to placebo, respectively, in 12-month randomized controlled trials of children.[114, 115, 117] Beclomethasone[114] was associated with a significantly higher risk of growth reduction (Table 14). Allen et al. reported no significant difference in change in height from baseline between the fluticasone aqueous 200 mcg and placebo groups.[115] The study of mometasone 100 mcg compared with placebo also showed no significant differences in mean height increase over 1 year.[117] Murphy, et al. found no significant mean difference in growth velocity from baseline to 1 year between budesonide (64 mcg/day) and

placebo. Finally, Skoner, et al. found a reduction in growth rate for beclomethasone aqueous 168 mcg twice daily when compared to placebo after 12 months.[114]

We are aware of unpublished interim results from a randomized open-label 52-week comparison of budesonide aqueous to cromolyn sodium in children with perennial rhinitis that suggest some progressive slowing of growth in the budesonide group (http://www.fda.gov/cder/foi/nda/96/020233s003_rhinocort_toc.htm).

Evidence from observational studies is inconsistent with the placebo-controlled trials. A retrospective study of 60 children (Age 24-117 months, mean age 70 months) taking beclomethasone aqueous 336 mcg/day for confirmed perennial rhinitis investigated medium and long-term growth and found no adverse growth effects.[123] It should be noted that this study was unable to determine compliance rates from the clinical records and the children were allowed to take other antiallergic medication (antihistamines and decongestants) as needed.

Another observational study examined long-term growth rates in 73 children using budesonide over a period of 24 months.[121] They assessed growth by comparing mean height to height predicted at entry. Changes in predicted mean heights after 12 and 24 months were not statistically significant.

Table 14. Summary of growth outcomes

Study Sample size Mean age % female	Interventions (Total daily dose) Duration	Outcome	Results
Skoner, 2000 N=80 7.5 years/7.1 years 31%	**Beclomethasone aqueous** (336 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline	5.0 cm compared with 5.9, *P*<0.01
Schenkel, 2000 N=98 6.3 years 32.7%	**Mometasone aqueous** (100 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3-5 years 6-9 years	7.65 cm compared with 7.26 cm 6.67 cm compared with 6.0 cm, both NS
Allen, 2002 N=150 6.2 years 34%	**Fluticasone p. aqueous** (200 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline 3 months completed 12 months completed	6.39 cm compared with 6.30 cm 6.32 cm compared with 6.20 cm, both NS
Mansfield, 2002 N=60 5.8 years 33%	**Beclomethasone aqueous** (168-336 mcg) Mean treatment duration: 3 years Retrospective observational	Comparison annual growth velocity with predicted growth velocity	Boys: 6.66 cm/y compared with6.0 cm/y Girls: 4.66 cm/y compared with 5.25 cm/y, both NS
Moller, 2003 N=78 10.8 years 28%	**Budesonide aerosol and aqueous** (200-600 mcg) 24 months Prospective open observational	Mean height percent of predicted at entry compared with actual mean height percent First 12 months: aerosol Second 12 months: aqueous Mean change in height from baseline First 12 months: aerosol Second 12 months: aqueous	102.5% compared with 102.2% 102.1% compared with 101.9%, both NS 4.9 cm compared with 5.2 cm
Murphy, 2006 N=229 5.9 years 34%	**Budesonide aqueous** (64 mcg) compared with placebo 12 months Randomized, double-blind, placebo-controlled	Mean change in height from baseline Mean growth velocity Mean difference in growth velocity	5.83 compared with 6.17 cm, NS 5.91 compared with 6.19 cm/year, NS 0.27 +/-0,18 cm/year (95%CI, -0.07 to 0.62 cm/year)

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications, or comorbidities, or in pregnancy and lactation for which one nasal corticosteroid is more effective or associated with fewer adverse events?

No studies stratified or analyzed data by subgroups of patients based on demographics, use of concomitant medications, or comorbidities. Race was only reported in one-third of all head-to-head trials and was predominantly Caucasian.[14, 19, 23, 25-27, 54, 97, 103, 113] Use of other concomitant nasal medications and/or presence of other concurrent nasal pathologies (e.g., sinusitis, viral infections, nasal structural abnormalities) were generally exclusionary. Given

these limitations, the demographic, concomitant medication usage, and comorbidity data provided can only be useful in determining the generalizability of results, but do not provide many insights into potential differences in efficacy or adverse events.

I. Demographics

Most head-to-head trials conducted in adults were comprised of comparable proportions of males (52%) and females (48%) and mean age overall was 33.5 years (range 24 years to 66.7 years). There were a few exceptions. One 4-week trial of mometasone 100 or 200 mcg and beclomethasone 400 mcg involved 477 adults with seasonal allergic rhinitis that were almost all male (91.5%).[29] Indirect comparisons suggest that physician ratings of improvement and changes in total symptom scores were similar in this trial to other similar trials with higher proportions of female participants. In another trial of flunisolide 200 mcg compared with beclomethasone 400 mcg in adults with seasonal allergic rhinitis and a noticeably higher mean age of 66.7, however, rates of physician-rated improvement were numerically lower than in other similar trials of younger patients.[20] It is not possible to draw conclusions about potential differential effects based on age using data from this trial, as the lower rates could also have been due to the use of a more stringent definition of improvement ("total" compared with "significant").

With regard to race, 1 study compared the adverse sensory attributes of fluticasone, mometasone, and triamcinolone in 364 adults with perennial allergic rhinitis who were all of Asian descent.[101] It is not possible to compare treatment effects in this trial to those reported in other similar head-to-head trials due to heterogeneity in outcome reporting. The only other evidence of safety and efficacy in an elderly population (65-87 years) with perennial allergic rhinitis was found in an unpublished 12-week placebo-controlled trial of mometasone identified in our dossier review. Mometasone 200 mcg/day was found to be significantly more effective than placebo in reducing total nasal symptom scores in the first 2 weeks. Local adverse effects such as headache, pharyngitis, coughing, and epistaxis occurred more frequently in the mometasone treatment group although statistical significance was not reported.[125]

Trials in children were comprised of more males (65%) than females and the mean age overall was 9 years. Similarly, trials of adolescents were comprised of mostly males (90%) and the mean age was 14 years.[38, 85, 88] The highest reported prevalence of male participants (97%) was reported in 1 of the trials of adolescents with seasonal allergic rhinitis that compared 2 weeks of treatment with fluticasone 100 or 200 mcg with placebo (N=243).[38] Rates of patients with significant improvement in this trial appear similar to those in other placebo-controlled trials of fluticasone and this evidence does not suggest that fluticasone has differential effects based on gender.

The only evidence of using nasal corticosteroids in very young children comes from placebo-controlled trials of fluticasone or mometasone. The first 6-week study found fluticasone safe and effective for 26 very young children between ages of 2 and 4 years with confirmed perennial rhinitis.[126] This randomized double-blind double-dummy placebo-controlled trial compared fluticasone 100 mcg and an oral placebo with ketotifen 1 mg (an antihistamine with mast-cell stabilizer activity) and a placebo nasal spray. The fluticasone treatment group showed statistically better efficacy for total nighttime and daytime symptom scores and for nasal blockage at 4-6 weeks. All other individual symptom scores revealed no significant differences between treatment groups. As a secondary outcome, investigators assessed 9 children using fluticasone to have experienced improvement or substantial improvement, while only 4 in the

ketotifen group had the same level of improvement. There were as well no significant differences in frequency of adverse events. Additional evidence of safety in young children between the ages 2-5 years comes from an unpublished placebo-controlled trial of mometasone that was revealed in our dossier review. There were no serious adverse events found during the 6-week treatment period and headache and rhinorrhea were more common in the placebo group, while upper respiratory tract infection and skin trauma occurred more frequently in children using mometasone.[125]

With regard to race, 1 placebo-controlled trial examined the potential growth suppression effects of beclomethasone AQ 336 mcg over 1 year in 80 children that were 57% black.[114] This data is only descriptive, however, and does not provide evidence of the comparative effects of beclomethasone relative to other nasal corticosteroids based on race.

II. Comorbidities

A. Asthma

Patients with comorbid asthma were included in 8 head-to-head trials in adults.[13, 16, 20, 21, 24, 50, 51, 56] None reported analyses of rhinitis symptom outcome in the subgroups of patients with asthma, however. Only 1 trial conducted any subgroup analyses of the patients with comorbid asthma, but the focus was only on asthma symptom outcomes.[13] This subgroup analysis involved patients with fall seasonal asthma and was conducted on 19 patients using flunisolide and 11 patients using beclomethasone nasal sprays.[13] The authors reported that baseline scores for chest symptoms were similar for both groups. During the peak of ragweed season the placebo-treated patients reported a 10-fold increase in symptoms compared to patients treated with nasal corticosteroids. The expected symptoms of asthma did not occur in most of the active treatment patients. The study was not designed for rigorous evaluation of asthma symptoms and patients were not screened with pulmonary function tests, nor was the asthma monitored throughout the trial with peak flow meters or spirometry.

One small (N=28), fair quality, randomized, placebo-controlled, double-blind crossover trial examining intranasal beclomethasone aqueous in pediatric patients (mean age 10 years) with perennial allergic rhinitis and concomitant asthma showed positive effects on rhinitis symptoms and mixed effects on asthma symptoms.[127] After 4 weeks, the mean rhinitis symptom scores were lower for those taking beclomethasone in the morning (P=0.06) and in the evening (P=0.03). In contrast, the morning asthma symptom scores were lower for beclomethasone at end of the study (P=0.07) but the evening scores were temporarily significantly lower in week 2 and 3, only to be similar at study end.[127]

Dahl, et al. investigated the cross effects of nasal and inhaled corticosteroids on both symptoms of pollen-induced rhinitis and asthma in a 6-week study with 262 patients receiving either only inhaled or nasal fluticasone, placebo, or combined therapy.[128] Results showed that nasal medication controlled nasal symptoms and inhaled medication controlled pulmonary symptoms but did not reduce reported symptoms in the untreated disease. The combined treatment did well in alleviating overall pollen-induced symptoms.

Another smaller 16-week active control study (N=59) looked at cross symptoms in patients with allergic rhinitis and mild-to-moderate asthma in 3 groups: nasal beclomethasone, inhaled beclomethasone, and combined treatment.[129] Results showed that self-assessed asthma symptom scores (from patient diaries) do improve significantly when treated with nasal

beclomethasone only (*P*=0.0001) and similarly for nasal symptoms treated with inhaled beclomethasone only (*P*=0.002). Using symptom scores from Asthma and Rhinitis Questionnaires, the asthma scores were significantly decreased (*P*=0.009) in all treatment groups, but not the rhinitis scores (*P*=0.09).

B. Daytime somnolence and/or sleep disorders

Five small (N=22 to 32) fair-quality, randomized, placebo-controlled, double-blind crossover trials examining patients with perennial allergic rhinitis and concomitant daytime somnolence and/or sleep disorders reported mixed efficacy of nasal corticosteroids in treating these comorbidities.[130-134] Due to heterogeneity in outcome reporting, data from these trials were insufficient for analyzing the indirect comparative efficacy and safety of fluticasone and budesonide on rhinitis symptom outcomes in patients with comorbid sleep disturbances.

Three of the trials studied fluticasone 200 mcg/day; the first found the active drug to be significantly better at improving subjective nasal congestion and daytime alertness (*P*=0.02) but found no difference in subjective sleep quality or partner-reported snoring between treatment groups.[131] The second fluticasone trial (Craig, et al.) reported significantly improved sleep as recorded by patients (*P*=0.04) but found no significant differences in nasal congestion, daytime sleepiness, and daytime fatigue between treatments.[132] Craig, et al. also found no significant differences in any of the 9 items in the quality of life questionnaire or subjective analysis of quality of sleep assessment.[132] The final study, Mansfield, et al., did not find any between-group differences in reaction time or daytime somnolence but did find a significant improvement in nasal congestion in the fluticasone group.[133]

The other 2 trials studied the use of budesonide aqueous 128 mcg/day in patients with confirmed perennial allergic rhinitis. In the Gurevich study (N=22), significant improvement was seen in self-assessed daytime sleepiness between treatment and placebo (*P*=0.01) and in the total subjective sleep measures score (*P*=0.04).[134] However, there was no significant improvement for the Epworth Sleepiness Scale, the Functional Outcome of Sleep Questionnaire, or the Rhinoconjunctivitis Quality of Life Questionnaire. Hughes, et al., study subjects (N=26) also had symptoms of daytime fatigue and somnolence and reported significant differences in change of symptom severity (reported on 5-point scale, 0=none and 4=severe) in favor of active drug for daytime sleepiness (*P*=0.02), daytime fatigue (*P*=0.03), and sleep problems (*P*=0.05), however not for nasal congestion (*P*=0.08).[130] There was no significant differences between treatment groups in the items from the Juniper's Rhino-conjunctivitis Quality of Life Questionnaire and the Functional Outcome of Sleep Questionnaire, although there were some numerical differences favoring the active drug.

III. Pregnancy

Fluticasone AQ 200 mcg and placebo had similar effects on pregnancy rhinitis symptoms in 53 women after 8 weeks in the only trial of such patients identified for inclusion in this review.[135] Study authors defined pregnancy rhinitis as nasal congestion of more than 6 weeks duration during pregnancy without other known causes, such as respiratory tract infection or allergy, and disappearing within 2 weeks of delivery. The primary efficacy variable was the measurement of nasal peak expiratory flow, which is not included in this review. The secondary outcome of mean weekly morning symptom scores revealed no significant difference between

fluticasone and placebo, 1.5 compared with 1.9 on a 4-point scale (0=none and 3=severe symptoms). Measured safety outcomes included delivery week, birth weight, femur length, and biparietal diameter. There were no significant treatment group differences in any of the adverse events.

A recently published systematic review reported on budesonide use in pregnancy.[136] This review included data from multiple observational studies and 1 randomized controlled trial and included patients with allergic rhinitis and asthma. None of the included studies compared budesonide to another nasal corticosteroid. Among the included studies, pregnancy outcomes, including stillbirth, congenital malformations, birth weight, and gestational age were not significantly affected by budesonide use either in early pregnancy or throughout pregnancy.

SUMMARY

Table 15 summarizes the main findings of this review.

Table 15. Summary of the evidence by key question

Key Questions 1 and 2: Efficacy and safety	Strength of evidence	Conclusions
Adults: Efficacy and common adverse effects		
Treatment of seasonal allergic rhinitis: Adults	Beclomethasone compared with others: Moderate Fluticasone compared with others: Moderate Flunisolide old compared with new or beclomethasone: Low Ciclesonide: Low Fluticasone furoate: Low	**Beclomethasone compared with budesonide, flunisolide, fluticasone, mometasone, triamcinolone**: Differences in efficacy or adverse events not found **Fluticasone compared with budesonide, triamcinolone:** Differences in efficacy or adverse events not found. **Flunisolide old compared with new, beclomethasone:** Differences in efficacy not found; old flunisolide associated with higher rates of burning/stinging Ciclesonide and fluticasone furoate: No direct evidence; data from PCTs confirm the efficacy of these drugs compared to placebo
Prophylaxis of seasonal allergic rhinitis: Adults	Mometasone compared with beclomethasone: Low	Mometasone associated with lower rhinitis symptom severity during pre- and peak-seasons; but increased risk of headache with mometasone
Treatment of perennial allergic rhinitis: Adults	Budesonide compared with others: Low Beclomethasone compared with fluticasone: Low Mometasone compared with others: Low Flunisolide new compared with old: Low	**Budesonide superior to fluticasone** in reducing combined nasal symptom score in 1 fair-quality trial; no differences in adverse events **Budesonide compared with mometasone**: Differences in efficacy or adverse events not found **Beclomethasone compared with fluticasone**: Differences in efficacy or adverse events not found when compared at equivalent dosage levels **Mometasone compared with beclomethasone, fluticasone:** Differences in efficacy or adverse events not found **Flunisolide new compared with old:** Differences in efficacy or adverse events not found
Treatment of non-allergic rhinitis	Very low overall: No head-to-head trials; indirect comparisons of fluticasone, mometasone from placebo-controlled trials	Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Adults: Serious harms		
Cataracts	Beclomethasone compared with non-use: Very low	No increase in the relative risk of cataract among all users of nasal corticosteroids (RR 1.0, 95% CI 0.6-1.4) or among beclomethasone users compared with the unexposed (RR 0.8, 95% CI 0.5-1.2) in 1 retrospective observational study

Other harms	Triamcinolone, mometasone, ciclesonide, fluticasone, fluticasone furoate: very low	No head-to-head studies compared long-term adverse event rates among the various nasal corticosteroids. Evidence is extremely limited and insufficient for indirect comparisons.
Children: Efficacy and common adverse effects		
Treatment of seasonal allergic rhinitis: Children	Mometasone compared with beclomethasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, flunisolide, fluticasone, triamcinolone: Very low	**Mometasone compared with beclomethasone:** Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Treatment of perennial allergic rhinitis: Children	Beclomethasone compared with fluticasone: Low Indirect comparisons from placebo-controlled trials of beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone: Very low	**Beclomethasone compared with fluticasone:** Differences in efficacy or adverse events not found Indirect comparisons from placebo-controlled trials: Provided no additional information about comparative efficacy/safety due to extreme heterogeneity
Treatment of non-allergic rhinitis: Children	No evidence found	
Children: Serious harms		
Growth retardation	Beclomethasone, fluticasone, mometasone, budesonide: Low	**Beclomethasone:** Significantly lower height increase over 12 months relative to placebo in 1 trial; similar to expected height increases over 3 years in a retrospective observational study **Fluticasone, mometasone, budesonide:** Similar height increases over 12 months relative to placebo
Lenticular opacities	Budesonide: Very low	Budesonide was associated with development of 2 cases of transient lenticular opacities in an uncontrolled retrospective study of 78 children over a 2-year period; the clinical significance of the opacities was not reported
Key Question 3: Subgroups	**Strength of evidence**	**Conclusions**
Demographics, concomitant medication use, comorbidities (asthma, daytime somnolence/sleep disorders), pregnancy rhinitis:	Very low	No conclusions about *comparative* effectiveness, efficacy or safety can be made.

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Appendix A. Search strategies

Original searches

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:

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1 mometasone.mp. (237)
2 fluticasone.mp. (1428)
3 budesonide.mp. or BUDESONIDE/ (1748)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
6 flunisolide.mp. (169)
7 corticosteroid$.mp. (5107)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
9 rhiniti$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
10 8 and 9 (757)
11 limit 10 to yr="2000 - 2005" (230)
12 from 11 keep 1-230 (230)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2005>
Search Strategy:

---

1 mometasone.mp. (237)
2 fluticasone.mp. (1428)
3 budesonide.mp. or BUDESONIDE/ (1748)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (694)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1429)
6 flunisolide.mp. (169)
7 corticosteroid$.mp. (5107)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (8660)
9 rhiniti$.mp. [mp=title, original title, abstract, mesh headings, heading words, keyword] (2935)
10 8 and 9 (757)
11 from 10 keep 1-757 (757)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>
Search Strategy:

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1 mometasone.mp. (244)
2 fluticasone.mp. (1388)
3 budesonide.mp. or BUDESONIDE/ (1882)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)

6 flunisolide.mp. (132)
7 1 or 2 or 3 or 4 or 5 or 6 (5171)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (45969)
9 exp ADMINISTRATION, INTRANASAL/ (3465)
10 8 and 9 (282)
11 7 or 10 (5291)
12 rhiniti$.mp. or exp RHINITIS/ (7952)
13 11 and 12 (518)
14 limit 13 to (humans and english language) (467)
15 limit 14 to yr="2000 - 2005" (277)
16 from 15 keep 1-277 (277)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:
---
1 mometasone.mp. (271)
2 fluticasone.mp. (1541)
3 budesonide.mp. or BUDESONIDE/ (2634)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
6 flunisolide.mp. (293)
7 1 or 2 or 3 or 4 or 5 or 6 (11520)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (164623)
9 exp ADMINISTRATION, INTRANASAL/ (6753)
10 8 and 9 (450)
11 7 or 10 (11730)
12 rhiniti$.mp. or exp RHINITIS/ (19048)
13 11 and 12 (1049)
14 limit 13 to (humans and english language) (915)
15 limit 14 to yr="1966 - 1999" (630)
16 from 15 keep 1-630 (630)

Database: Ovid MEDLINE(R) <1966 to October Week 2 2005>
Search Strategy:
---
1 mometasone.mp. (271)
2 fluticasone.mp. (1541)
3 budesonide.mp. or BUDESONIDE/ (2634)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (5443)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (2761)
6 flunisolide.mp. (293)
7 corticosteroid$.mp. (44658)

8 exp adrenal cortex hormones/ (135755)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (171616)
10 (nasal$ or nose or intranasal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (80991)
11 (ae or po or to or ct).fs. (1100937)
12 (advers$ adj5 effect$).mp. (59983)
13 11 or 12 (1132475)
14 9 and 10 and 13 (681)
15 limit 14 to (humans and english language) (585)
16 limit 15 to yr="2000 - 2005" (190)
17 15 not 16 (395)
18 from 17 keep 1-395 (395)

Database: Ovid MEDLINE(R) <1996 to October Week 1 2005>
Search Strategy:
---
1 mometasone.mp. (244)
2 fluticasone.mp. (1388)
3 budesonide.mp. or BUDESONIDE/ (1882)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (1407)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1182)
6 flunisolide.mp. (132)
7 corticosteroid$.mp. (20122)
8 exp adrenal cortex hormones/ (31448)
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (48857)
10 (nasal$ or nose or intranasal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (33204)
11 (ae or po or to or ct).fs. (427255)
12 (advers$ adj5 effect$).mp. (34224)
13 11 or 12 (445407)
14 9 and 10 and 13 (351)
15 limit 14 to (humans and english language) (305)
16 limit 15 to yr="2000 - 2005" (185)
17 from 16 keep 1-185 (185)

Update #1 searches

Database: Ovid MEDLINE(R) <1996 to September Week 1 2007>
Search Strategy:
---
1 mometasone.mp. (308)
2 fluticasone.mp. (1769)
3 budesonide.mp. or BUDESONIDE/ (2273)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (2134)

5 beclomethasone.mp. or exp BECLOMETHASONE/ (1363)
6 flunisolide.mp. (149)
7 1 or 2 or 3 or 4 or 5 or 6 (6741)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, name of substance word, subject heading word] (93518)
9 exp ADMINISTRATION, INTRANASAL/ (4327)
10 8 and 9 (520)
11 7 or 10 (6961)
12 rhiniti$.mp. or exp RHINITIS/ (10294)
13 11 and 12 (647)
14 limit 13 to (humans and english language) (579)
15 (20051$ or 2006$ or 2007$).ed. (1242454)
16 14 and 15 (105)
17 from 16 keep 1-105 (105

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2007>
Search Strategy:
---
1 mometasone.mp. (279)
2 fluticasone.mp. (1586)
3 budesonide.mp. or BUDESONIDE/ (1851)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (777)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (1450)
6 flunisolide.mp. (174)
7 1 or 2 or 3 or 4 or 5 or 6 (5340)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, original title, abstract, mesh headings, heading words, keyword] (11428)
9 exp ADMINISTRATION, INTRANASAL/ (1478)
10 8 and 9 (244)
11 7 or 10 (5380)
12 rhiniti$.mp. or exp RHINITIS/ (3673)
13 11 and 12 (792)
14 limit 13 to yr="2005 - 2007" (54)
15 from 14 keep 1-54 (54)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2007>
Search Strategy:
---
1 mometasone.mp. (18)
2 fluticasone.mp. (66)
3 budesonide.mp. or BUDESONIDE/ (81)
4 exp TRIAMCINOLONE/ or triamcinolone.mp. (74)
5 beclomethasone.mp. or exp BECLOMETHASONE/ (66)
6 flunisolide.mp. (41)

7 1 or 2 or 3 or 4 or 5 or 6 (131)
8 corticosteroid$.mp. or exp adrenal cortex hormones/ [mp=title, abstract, full text, keywords, caption text] (642)
9 [exp ADMINISTRATION, INTRANASAL/] (0)
10 8 and 9 (0)
11 7 or 10 (131)
12 rhiniti$.mp. or exp RHINITIS/ (103)
13 11 and 12 (18)
14 limit 13 to yr="2005 - 2007" (11)
15 from 14 keep 1-11 (11)

Appendix B. Quality criteria

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination[10, 11] criteria.

All studies regardless of design, that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw are rated poor quality. A fatal flaw is reflected in failing to meet combinations of criteria, which may be related in indicating the presence of bias. An example would be failure or inadequate procedures for randomization and/or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality and the remainder is rated fair quality. As the "fair" quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are likely to be valid, while others are only probably valid. A "poor quality" trial is not valid-the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the 4 components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the

process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).
For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    Adequate approaches to sequence generation:
        Computer-generated random numbers
        Random numbers tables
    Inferior approaches to sequence generation:
        Use of alternation, case record numbers, birth dates or week days
    Not reported

2. Was the treatment allocation concealed?
    Adequate approaches to concealment of randomization:
        Centralized or pharmacy-controlled randomization
        Serially-numbered identical containers
        On-site computer based system with a randomization sequence that is not readable until allocation
        Other approaches sequence to clinicians and patients

Inferior approaches to concealment of randomization:
- Use of alternation, case record numbers, birth dates or week days
- Open random numbers lists
- Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

Non-randomized studies:
Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainers; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

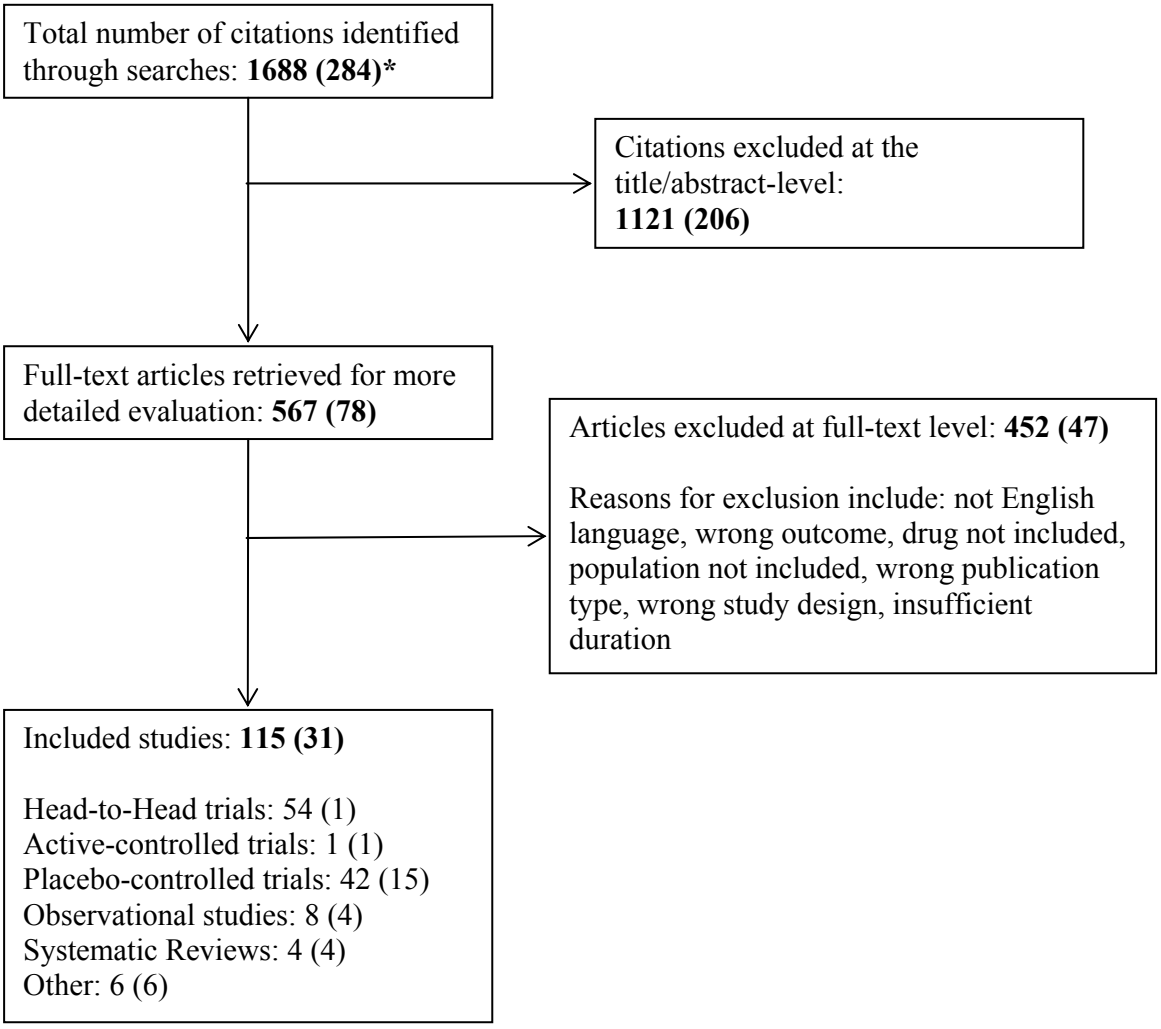
2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Appendix C. Results of literature search



* Totals in parenthesis reflect results of literature search specific to update 1

Appendix D. Listing of excluded studies

Excluded studies	Reasons for exclusion
Active-controlled trials	
Khanna P, Shah A. Assessment of sensory perceptions and patient reference for intranasal corticosteroid sprays in allergic rhinitis. *American Journal of Rhinology.* May-Jun 2005;19(3):316-321.	Outcome not included
Barnes ML, Biallosterski BT, Gray RD, Fardon TC, Lipworth BJ. Decongestant effects of nasal xylometazoline and mometasone furoate in persistent allergic rhinitis. Rhinology. Dec 2005;43(4):291-295.	Study design not included
Bhatia S, Baroody FM, deTineo M, Naclerio RM. Increased nasal airflow with budesonide compared with desloratadine during the allergy season. *Archives of otolaryngology--head & neck surgery.* Mar 2005;131(3):223-228.	Study design not included
Cordray S, Harjo JB, Miner L. Comparison of intranasal hypertonic dead sea saline spray and intranasal aqueous triamcinolone spray in seasonal allergic rhinitis. *Ear, Nose, & Throat Journal.* Jul 2005;84(7):426-430.	Study design not included
Das S, Gupta K, Gupta A, Gaur SN. Comparison of the efficacy of inhaled budesonide and oral choline in patients with allergic rhinitis. *Saudi medical journal.* Mar 2005;26(3):421-424.	Study design not included
Zieglmayer UP, Horak F, Toth J, Marks B, Berger UE, Burtin B. Efficacy and safety of an oral formulation of cetirizine and prolonged-release pseudoephedrine versus budesonide nasal spray in the management of nasal congestion in allergic rhinitis. *Treatments in Respiratory Medicine.* 2005;4(4):283-287	Study design not included
Placebo-controlled trials	
Barnes ML, Biallosterski BT, Fujihara S, Gray RD, Fardon TC, Lipworth BJ. Effects of intranasal corticosteroid on nasal adenosine monophosphate challenge in persistent allergic rhinitis. *Allergy.* Nov 2006;61(11):1319-1325.	Outcome not included
Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. *Journal of Allergy & Clinical Immunology.* May 2005;115(5):940-945.	Intervention not included
Gradman J, Caldwell MF, Wolthers OD. A 2-week, crossover study to investigate the effect of fluticasone furoate nasal spray on short-term growth in children with allergic rhinitis. C*inical therapeutics.* Aug 2007;29(8):1738-1747.	Population not included
Nave R, Wingertzahn MA, Brookman S, Kaida S, Matsunaga T. Safety, tolerability, and exposure of ciclesonide nasal spray in healthy and asymptomatic subjects with seasonal allergic rhinitis. *Journal of Clinical Pharmacology.* Apr 2006;46(4):461-467.	Population not included

Excluded studies	Reasons for exclusion
Rowe-Jones JM, Medcalf M, Durham SR, Richards DH, Mackay IS. Functional endoscopic sinus surgery: 5 year follow up and results of a prospective, randomised, stratified, double-blind, placebo controlled study of postoperative fluticasone propionate aqueous nasal spray. *Rhinology.* Mar 2005;43(1):2-10.	Population not included
Observational studies	
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Appendix E. Adverse effects in head-to-head trials

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasarritation
Al-Mohaimeid 1993 N=120 3 wks	30 years 27.5% PAR	BUD 400 µg vs. BEC 400	5.2% vs. 1.7%; NS	NR	NR	NR	NR
Bende 2002 N=438 4 wks	31.0 years 57.7% PAR	MOM 200 vs. BUD 256/128	1.9% vs. 4.7% vs. 0.9%; NS	9% vs. 11% vs. 11%; NS	NR	6% vs. 9% vs. 6%; NS	NR
Berger 2003 3 wks N=295	31.6 yrs 62% SAR	TRI AQ 220 vs. FLUT 200	None	6.8% vs. 4.1%, NS	Pharyngitis: 0.7% vs. 2.7%; NS	2.7% vs. 4.8%, NS	NR
Bronsky 1987 N=151 4 wks	29 yrs 52% SAR	FLUN 200/300 vs. BEC 168/336	NR	10% vs. 10% vs. 12% vs. 10%, NS	8% vs. 5% vs. 5% vs. 0%, NS	8% vs. 8% vs. 7% vs. 8%, NS	Stinging/burning: 30% vs. 33% vs. 10% vs. 10%; *P*<0.05
Bunnag 1984 N=45 4 wks	28.5 years 66.7% PAR	FLUN 200 vs. BEC 400	2.2% vs. 0; NS	2.2% vs. 2.2%; NS	NR	NR	Burning sensation: 20% vs. 2.2%; *P*= 0.0081 Nasal irritation: 2.2% vs. 0; NS
Conley 1994 N=100 1 day	40.0 years 61% PAR	FLUN 50 vs. BEC 84	None	0 vs. 2%; NS	NR	NR	NR
Day 1998 N=273 6 wks	30.8 years 54.9% PAR	BUD 256 vs FLUT 200	1.8% vs. 1.8%; NS	9% vs. 10%; NS	NR	Bloody nasal discharge: 18% vs. 7%; NS	NR
Drouin 1996 N=427 12 wks	31.7 years 45.4% PAR	MOM 200 vs. BEC 400	5.6% vs. 4.1%; NS	10% vs. 7%; NS	Pharyngitis: 4% vs. 6%; p-value NR	19% vs. 23%; NS	Nasal irritation: 3% vs. 3%; NS Nasal Burning: 3% vs. 3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasarritation
Graft 1996† N=347 8 wks	34.7 yrs 47.3% SAR	MOM 200 vs. BEC 336	0.8% vs. 4.3%; NS	36% vs. 22%; *P*=0.02‡	Pharyngitis: 6% vs. 10%; NS	NR	NR
Greenbaum 1988 N=122 4 wks	NR NR SAR	New vs. old FLUN 200	2.4% vs. 4.1%; NS	<12% overall; NS between groups (data NR)	Throat irritation: 2% vs. 0; NS	NR	Severe nasal burning/stinging: 0 vs. 13%; *P*<0.001
Gross 2002 N=352 3 wks	38.8 yrs 66.5% SAR	TRI AQ 220 vs. FLUT 200	1.2% vs. 0; NS	11% vs. 11.7%; NS	Pharyngitis: 2.3% vs. 6.7%; NS	NR	NR
Haye 1993 N=242 ≤ 1 year	37.6 years 56.6% PAR	FLUT 200 vs. BEC 200	NR	8% vs. 4%; NS	NR	14% vs. 5%; *P*=0.0285	NR
Hebert 1996 N=477 4 wks	32 yrs 8.5% SAR	MOM 100/200 vs. BEC 400	3% vs. 4% vs. 0; NS	8% vs. 10% vs. 8%; NS	Pharyngitis: 3% vs. 2% vs. 4%, NS	3% vs. 6% vs. 5%, NS	NR
Laforce 1994 N=238 4 wks	24 yrs 29% SAR	FLUT 200 BID or QD vs. BEC 336	0 vs. 0 vs. 1.6%; NS	4.7% vs. 3.6% vs. 4.9%, NS	3.1% vs. 0 vs. 3.3%, NS	0 vs. 1.8% vs. 4.9%; NS	Burning: 1.6% vs. 1.8% vs. 6.5%; NS
Langrick 1984 N=60 7 wks	66.7 yrs 37.5% SAR	FLUN 200 vs. BEC 400	None	Dry throat: 2.9% vs. 0; NS Tickling sensation in nose: 0 vs. 2.8%; NS			
Lumry 2003 N=147 3 wks	37 yrs 51% SAR	TRI AQ 220 vs. BEC 336	None	Respiratory system: 15% vs. 10%; skin and appendages: 1% vs. 9%; digestive system: 5% vs. 5%; nervous system: 4% vs. 0; all *P*=NS			
Mandl 1997 N=550 3 mo	33.0 years 54.7% PAR	MOM 200 vs. FLUT 200	1% vs. 2%; NS	6% vs. 9%; NS	NR	17% vs. 17%; NS	Nasal burning: 3% vs. 3%; NS Nasal irritation: 2% vs. 3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasarritation
McArthur 1994 N=77 3 wks	27 yrs 51% SAR	BUD 200 vs. BEC 200	4% vs. 0; NS	2% vs. 0; NS	2% vs. 0; NS	0 vs. 2.6%; NS	Itchy nose: 0 vs. 2.6%; NS
Ratner 1992 N=136 2 wks	44 yrs 62% SAR	FLUT 200 vs. BEC 336	None	0 vs. 1%; NS	2% vs. 2%; NS	3% vs. 2%; NS	Nasal burning: 5% vs. 2%; NS
Ratner 1996 N=218 6 wks	44 yrs 62% SAR	New vs. old FLUN 200	NR	9% vs. 5%; NS	NR	NR	Irritation/tenderness: 4% vs. 4%; NS
Sahay 1980 N=60 4 wks	37 yrs 48% PAR	FLUN 200 vs. BEC 400	3.3% vs. 10%; NS	13.3% vs. 3.3%; NS	NR	0 vs. 10%; NS	Nasal irritation: 10% vs. 3.3%; NS Nasal dryness: 6.7% vs. 10%; NS
Small 1997 N=233 3 wks	28 yrs 52% SAR	TRI HFA 220 vs. FLUT 200	NR	5% vs. 9%; NS	NR	3% vs. 4%; NS	NR
Stern 1997 N=635 4-6 wks	Age NR 51% SAR	BUD 128/256 vs. FLUT 200	0.5% vs. 0.5% vs. 1.7%; NS	NR	NR	NR	NR
Synnerstad 1996 N=25 12 mo	44.1 years 16% NAR	BUD 256 vs. BEC 336	NR	NR	NR	0 vs. 25%	8.3% vs. 16.6%; p-value NR
Tai 2003 N=24 8 wks	40.9 years 62.5% PAR	BUD 400 vs FLUT 200	None	NR	NR	NR	NR
van As 1993 N=466 6 mo	36.3 years 51.3% PAR	FLUT 200 BID/200 QD vs. BEC 168	5% vs. 3% vs. 9%; NS	4% vs. 2% vs. 5%; NS		14% vs. 15% vs. 9%; NS	Nasal irritation: 0 vs. 2% vs. 0 Nasal dryness: 3% vs. 2% vs. 0; NS Nasal burning: 1% vs. 3% vs. 3%; NS
Welsh 1987 N=100 6 wks	28 yrs 33% SAR	FLUN 200 vs. BEC 336	6.7% vs. 0; NS	0 vs. 16.7%; *P*=0.0522	NR	Nosebleeds: 0 vs. 0	Sore nose: 3.3% vs. 3.3%; NS

Study Sample size Trial duration	Age % female Rhinitis type	Treatments (total daily dose in mcg)	Withdrawals due to adverse events	Headache	Throat soreness	Epistaxis	Nasarritation
Zawisza 1992 N=43 4 wks	NR NAR	FLUN 200 vs. BEC 300	0% vs. 10%	NR	NR	NR	20% vs. 40%; p-value NR

†Prophylaxis trial; ‡Fisher's exact test performed using StatsDirect (CamCode, U.K.)

Drug Class Review

Nasal Corticosteroids

Final Report Update 1
Evidence Tables

June 2008

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Berger 2003 USA (Fair) ---------- Kaiser 2004 USA	Parallel-group, single-blind, RCT Multicenter	Adult and adolescents with spring SAR for at least 24 mos. Positive epicutaneous or intradermal test to one or more of grass or tree pollen and/or outdoor molds TNSS (the sum of discharge, stuffiness, itching, and sneezing scores recorded the morning of randomization visit plus scores from 3 of the 4 previous days were required to equal at least 42 (of a possible 84) points for patients to continue in the study.	TAA AQ 220 mcg daily FP 200 mcg daily Study duration: 3 weeks	Wash-out period x 5 days involving discontinuation of all rhinitis medications Run-in: none	NR

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Berger 2003 USA (Fair) ---------- Kaiser 2004 USA	Patient reported severity (0=absent to 3=severe of nasal symptoms (nasal drainage, stuffiness, itching, and sneezing) scores twice daily during wash-out period through week 3 Primary outcome: TNSS (sum of individual symptom scores-max=12) RQLQ (patients >17 years of age) baseline and week 3 SAQ at week 3	Mean age (years): 31.6 % Female: 62 Race (%): White 81.7 Black 10.2 Other 8.1	TAA AQ vs. FP Years with allergic rhinitis Mean: 16.6 vs. 19.1 TNSS at baseline Mean: 8.06 vs. 7.64 ---------- Moderate severity (<8.14)(n=69 vs n=76) mean score :6.14 and 6.22 Severe (> or equal to 8.14) (n=79 vs n=71) mean score:10.03 vs 9.47	NR/NR/295	8 (2.7%)/4/ INSS n=290, RQLQ n=232 For Kaiser INSS/TNSS= 295, RQLQ=292

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Berger 2003 USA (Fair) ---------- Kaiser 2004 USA	**TNSS** TAA AQ=FP (data NR) TNSS moderate: TAA AQ (n=69) =39% improvement from baseline vs FP (n=76)=36% improvement from baseline (p=NS) TNSS severe: TAA AQ (n=79)=38% improvement from baseline vs FP (n=71)=41% improvement from baseline (p=NS) INSS moderate and severe difference in mean change from baseline was statistically significant TAA AQ=FP (p=NS) **INSS** (mean estimated from graph): N**asal discharge**: -0.76 vs -0.76 (p=NS) N**asal stuffiness:** -0.80 vs -0.78 (p=NS) **Sneezing:** -0.78 vs -0.80 (p=NS) **Nasal itching:** -0.85 vs -0.88 (p=NS) **RQLQ:** (TAA AQ n=110, FP n=122) Mean overall score: TAA AQ=FP (data NR) RQLQ moderate (TAA AQ n=58) vs (FP n=67): -1.9 vs -1.8 (p<0.0001) RQLQ severe (TAA AQ n=89) vs (FP n=78): -2.4 vs -2.3 (p<0.0001) **SAQ**: less odor reported with TAA AQ than FP (P<0.0001) *Moderate severity: < 8.14 baseline score Severe: > or equal to 8.14 baseline score

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Berger 2003 USA (Fair) ---------- Kaiser 2004 USA	Reported by patient Responses to 2 SAQ items prospectively defined as "treatment-related adverse events" (e.g. nose bleeds, nasal irritation)	TAA AQ (n=148) vs FP (n=147) (any causality, (%); possibly related, (%)) Headache: 10 (6.8) vs 6 (4.1); 2 (1.4) vs 1 (0.7) Epistaxis: 4 (2.7) vs 7 (4.8);3(2) vs 6 (4.1) Rhinitis: 3 (2) vs 6 (4.1); 3 (2) vs 4 (2.7) Infection: 2 (1.4) vs 5 (3.4); 0 vs 0 Pain: 4 (2.7) vs 2 (1.4); 0 vs 0 Sinusitis: 3 (2) vs 0; 0 vs 0 Back pain: 1 (0.7) vs 3 (2); 0 vs 0 Pharyngitis: 1 (0.7) vs 4 (2.7); 0 vs 2 (1.4) Cough increased:1 (0.7) vs 3 (2); 0 vs 1 (0.7) Accidental injury: 0 vs 3 (2); 0 vs 1 (0.7)	Withdrawals (overall): 8 Withdrawals (adverse events): 0	Kaiser re-analyzed Berger et al data to examine the effects of each drug on symptoms and HRQL in patients stratified into cohorts based on symptom severity.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Gross 2002 USA (Fair)	Parallel-group, single-blind, RCT Multicenter	Adult and adolescents with fall (ragweed) AR for at least 24 months. Positive skin prick test for ragweed. TNSS (the sum of discharge, stuffiness, itching, and sneezing scores recorded the morning of randomization visit plus scores from 3 of the 4 previous days were required to equal at least 42 (of a possible 84) points for patients to continue in the study.	TAA AQ 220 mcg daily FP 200 mcg daily Study duration: 3 weeks	Wash-out period x 5 days involving discontinuation of all rhinitis medications Run-in: none	No

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gross 2002 USA (Fair)	Patient reported nasal symptom scores (nasal discharge, stuffiness, itching; sneezing; ocular itching/tearing/redness) twice daily during wash-out period through week 3 RQLQ baseline and week 3	Mean age (years): 38.8 Female gender (%): 66.5 Race (%): Caucasian 81.3 Black 4.25 Asian 0.85 Hispanic 12.75 Other 0.85	TAA AQ vs FP TNSS at baseline Mean: 8.95 vs 9.01	NR/NR/352	10/NR/ unclear for INSS, safety n= 352. RQLQ n= 349

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Gross 2002 USA (Fair)	TAA AQ vs FP **TNSS:** 49.4% vs 52.7% change from baseline scores at wk 3 (p=NS) **INSS:** TAA AQ=FP (P=NS) in all INSS categories except FP provided greater reduction in sneezing at week 2 (P=0.046) **HRQL:** TAA AQ (n=170) vs FP (n=179) TAA AQ=FP (p=NS) **RQLQ**: individual dimensions TAA AQ = FP (p=NS) except emotions in which FP demonstrated significant improvement (P=0.04)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Gross 2002 USA (Fair)	Reported by patient via daily questionnaires	TAA AQ (n=172) vs FP (n=180) (possibly related, (%); probably related, (%)): Body as a whole: 2 (1.2) vs 3 (1.7); 0 vs 2 (1.1) Headache: 2 (1.2) vs2 (1.1); 0 vs 2 (1.1) Digestive system: 1 (0.6) vs 1 (0.6); 1 (0.6) vs 1 (0.6) Dyspepsia:0 vs 1 (0.6); 0 vs 0 Respiratory system:6 (3.5) vs 7 (3.9); 4 (2.3) vs 5 (2.8) Pharyngitis:1 (0.6) vs 2 (1.1); 0 vs 0 Rhinits:4 (2.3) vs 2 (1.1); 3 (1.7) vs 3 (1.7) Skin and appendages: 35 (20.3) vs 32 (17.8); 82 (47.6) vs 102 (56.7) Application (local) reaction 36 (21) vs 32 (17.8); 81 (47) vs 102 (56.7)	Withdrawals (overall): 10 Withdrawals (adverse events): 2 Two patients in the TAA group withdrew from the study, one patient due to nausea and the other due to nasal dryness, sinus dryness, and insomnia	Application reaction included post-dose burning, stinging, sneezing, or blood in mucus. Outcomes for INSS and TNSS is not reported. Raw data for INSS and TNSS is only reported in a bar graph which is very small so estimating actual numbers would be difficult.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Ratner 1992 USA (Fair)	Placebo-controlled Double-blind RCT Multicenter	Adult patients with moderate to severe SAR for at least 24 months Positive skin test to Mountain Cedar, *Juniperus ashei* Normal adrenal function Women of non-childbearing potential At least 200/400 points on INSS on at least 4 out of 7 days of run-in period	FP 200 mcg in the morning + placebo in the evening BDP 168 mcg twice daily Placebo twice daily Study duration: 2 weeks	Run-in period 4-14 days Wash-out: none	Chlorpheniramine 4 mg tablets

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ratner 1992 USA (Fair)	Nasal exam days 1, 8, and 15 and day 22 of post-treatment f/u INSS severity (nasal obstruction, rhinorrhea, sneezing, and itching) scored by clinician at each visit and by pts at the end of each day(scale of 0 (no symptoms) to 100 (severe symptoms)) Pt reported nasal obstruction upon awakening each day Clinician rated overall effectiveness (7 pt scale) at the end of study Morning plasma cortisol, exam, lab tests, 12-lead ECGs at screening visit and after 2 wks of treatment.	Mean age (years): 37.1 Female gender (%): 45.3 Race not reported	FP vs BDP vs PL asthma, n (%): 27(25) vs 24 (23) vs 20 (19) perennial rhinitis, n (%) 72(68) vs 53(51) vs 58(56) seasonal rhinitis (other than to mountain cedar), n (%) 59(56) vs 61(59) vs 63(61)	NR/NR/NR	4/NR/313

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Ratner 1992 USA (Fair)	FP vs BDP vs PL **INSS** (clinician-rated, patient-rated): For all INSS FP=BDP>PL (P<0.05 for both drugs vs placebo) **Nasal obstruction:** -0.32 vs -0.33 vs -0.23 -0.34 vs -0.37 vs -0.26 **Rhinorrhea:** -0.46 vs -0.44 vs -0.26 -0.38 vs -0.41 vs -0.20 **Sneezing:** -0.36 vs -0.39 vs -0.25 -0.35 vs -0.41 vs -0.19 **Nasal Itching:** -0.42 vs -0.43 vs -0.30 -0.35 vs -0.41 vs -0.24 **Nasal obstruction upon awakening:** FP=BDP on day 2 (p<0.05) and throughout treatment (p<0.01) **Overall efficacy (clinician rated):** FP=BDP>PL (P<0.001)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Ratner 1992 USA (Fair)	Elicited by investigator at each clinic visit	FP (n=106) vs BDP (103) vs PL (n=104) Sore throat: 2(2%) vs 2 (2%) vs 1 (1%) Blood in nasal mucus: 6(6%) vs 1(1%) vs 2(%) Nasal burning: 5(5%) vs 2(2%) vs 4(4%) Epistaxis: 3(3%) vs 2(2%) vs 0 Headache: 0 vs 1(1%) vs 3(3%) Any event: 19(18%) vs 10(10%) vs 19(18%)	Withdrawals (overall): 4 Withdrawals (adverse events): 2 (placebo group for insomnia, objectionable odor of study drug)	Authors only listed adverse events if reported by 3 or more patients across treatment groups All centers were in Texas with an allergen specific to that region. Treatment period was 2 weeks.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Graft 1996 USA (Fair)	Placebo-controlled Double-blind Parallel group RCT Multicenter	Adult and adolescent (at least 12 years old) pts with SAR for at least 24 months Positive skin prick test to ragweed Women of non-childbearing status or using acceptable form of birth control Free of nasal and non-nasal symptoms (score less than or equal to 1) and TNSS less than or equal to 2 at screening and baseline.	MF 200 mcg in the morning + placebo in the evening BDP 168 mcg twice daily Placebo twice daily Study duration: 8 weeks	Run-in period: none Wash-out period: 1 day to stop nasal, oral, or ocular decongestants. Oral antihistamines for a variable amount of time depending on duration of action Systemic corticosteroids for 1 month (IM or intraarticular for 3 months), nasal or ocular corticosteroid medications or cromolyn for 2 weeks	No

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Graft 1996 USA (Fair)	INSS : 4 nasal symptoms (rhinorrhea, nasal stuffiness/congestion, nasal itching, and sneezing) and 4 non-nasal symptoms (eye itching/burning, eye tearing/watering, eye redness, itching of ears/palate) using a 4-point rating scale. MD evaluated INSS on screening, day 1 (baseline), and days 8, 22, 29, 36, 50, 57 and the patient evaluated twice daily in a diary. Global Evaluation by patient and MD at each visit Compliance evaluated with phone call day 15 and 43 Adverse events (safety) reviewed with MD at each visit.	Mean age (years): 34.7 Female gender (%):47 Race (%): Caucasian: 93 Black: 3.3 Other: 2.7	Mean duration of disease (years): 19 for all 3 groups Patients entered the study an average of 23 days before onset of ragweed season symptoms.	NR/NR/349	2/NR/330 for efficacy, 347 for safety

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Graft 1996 USA (Fair)	MF (n=114) vs BDP (n=112) vs PL (n=104) The average proportion of minimal symptom days (am and pm scores averaged < or = 2) from the start of ragweed season to study completion: 0.83 vs 0.77 vs 0.64 MF=BDP>PL (p<0.01) The average proportion of minimal symptom days from the start of treatment to study completion: MF=BDP>PL (p<0.01) (numbers not reported) Number of days from start of ragweed season to a non-minimal symptom day (TNSS >/= 3): Median reported in text: 27 vs 27 vs 10.5 Fig.2 % pts with minimal symptoms at day 44: 39 vs 29 vs 29 Number of days to first occurrence of a non-minimal symptom day from start of treatment: 51.5 vs 50 vs 34 MF=BDP>PL (p=<0.01) **TNSS based on diary data** (mean change from baseline-start of ragweed season): Days 1-15 (estimated from graph): 0.4 vs 0.6 vs 1.4 MF=BDP>PL (p>0.01) Days 16-30 (estimated from graph): 0.8 vs 1.1 vs 2 MF=BDP>PL (p>0.01) Days 31-45 (estimated from graph): 0.9 vs 1.3 vs 2 MF=BDP>PL (p>0.01) **Investigator NSS change from baseline(all results estimated from graph** :) Day 8: 0.1 vs 0 vs 0.1 MF=BDP=PL Day 15: 0.4 vs 0.4 vs 0.75 MF=BDP=PL Day 29: 0.8 vs 0.7 vs 1.2 MF=BDP>PL (p>0.01) Day 36: 1.2 vs 1.4 vs 2.9 MF=BDP>PL (p>0.01) Day 50:1.2 vs 1.1 vs 2.4 MF=BDP > PL (p>0.01)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Graft 1996 USA (Fair)	Elicited by investigator at each clinic visit	MF (n=116) vs BDP (n=116) vs PL (n=115) Any adverse event, n (%): 73 (63) vs 59 (51) vs 60 (52) Headache, n (%): 42 (36) vs 25 (22) vs 27 (23) Pharyngitis, n (%): 7 (6) vs 12 (10) vs 6 (5) Upper respiratory tract infection, n (%): 7 (6) vs 3 (3) vs 1 (<1%) Dysmenorrhea*, n (%): 4 (6) vs 0 vs 4 (8%) *percents calculated based on total female population	Withdrawals (overall): 27 Withdrawals (adverse events): 10 (MF=1, BDP=5, PL=4)	Authors only listed adverse events if reported by 5% or more patients across treatment groups Study evaluated the use of MF and BDP as prophylactic agent for SAR Pollen counts collected from each center Typos in figure 2 (key) and table IV dose of BDP Statements in text don't seem to match text with regard to Fig.2. MF had less severe symptoms at baseline until the start of the season.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
McArthur 1994 UK (Fair)	Single-blind Parallel group RCT	Adult pts with a history of at least 2 seasons of SAR At least 2 defined seasonal allergic rhinitis symptoms (blocked nose, runny nose, itchy nose, or sneezing)	BUD 200 mcg twice daily BDP AQ 200 mcg twice Study duration: 3 weeks	Run-in: NR Wash-out: NR	antazoline-xylometazoline eye drops

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
McArthur 1994 UK (Fair)	INSS: recorded daily by pt: runny nose, blocked nose, sneezing, itchy nose, sore eyes, runny eyes (0-no symptoms to 3-severe symptoms) INSS: Clinician visit at entry Global assessment of study medication by pt at wk 3 AE reported by pt in diary card	Mean age (years):27 Female gender (%): 51 Race not reported	Mean duration of disease (years):10 Mean symptom score at baseline: BUD (n=50) vs BDP (n=38) Blocked nose: 1.6 vs 1.39 Runny nose: 1.96 vs 1.95 Itchy nose: 1.43 vs 1.66 Sneezing: 2.06 vs 2.03 P=NS for all INSS at baseline	NR/NR/88	22/NR/77 for efficacy, 88 for safety,73 for global effectiveness survey

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
McArthur 1994 UK (Fair)	Mean symptom score for entire treatment period: BUD (n=41) vs BDP (n=36) Blocked nose: 0.39 vs 0.55 (p=NS) Runny nose: 0.38 vs 0.66 (p= 0.01) Itchy nose: 0.3 vs 0.60 (p=0.01) Sneezing: 0.45 vs 0.92 (p<0.001) For mean total weekly scores during wk 1: BUD=BDP (p=NS) wk 2: BUD<BDP (p<0.005) wk 3: BUD<BDP (p<0.005) Global efficacy at end of treatment BUD (n=41) vs BDP (n=33) Noticeably, very or totally effective: 35 (85%) vs 27 (82%)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
McArthur 1994 UK (Fair)	Reported by pt	BUD (n=50) and BDP (n=38) Adverse event: n (%) Coughing: 2 (4) vs 0 Headache: 1 (2) vs 0 Nose Bleed:0 vs 1 (2.6) Sneezing: 1 (2) vs 0 Peculiar taste: 1 (2) vs 0 Slight wheezing: 2 (4) vs 0 Nausea/sickness: 0 vs 1 (2.6) Itching: 0 vs 1 (2.6) Diarrhea: 0 vs 1 (2.6) Chest tightness: 1(2) vs 0 Itchy nose: 0 vs 1 (2.6) Sore throat: 1 (2) vs 0 Total: 9 (18) vs 5 (13)	Withdrawals (overall): 22 BUD: 14, (25%) BDP: 8, (21%) Withdrawals (adverse events): 2 (BUD: sneezing and coughing/wheezing)	No SPT for eligibility Other withdrawals were due lack of efficacy, unassociated illness, or refusal to cooperate Withdrawals 22/88 (25%) 11/22 withdrew due to refusal to cooperate.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Langrick 1984 England (Fair)	Single-blind Parallel group RCT Number or Centers: NR	Adult pt with history of moderate to severe hay fever Agreed to treatment during the same 7-week period (May-July)	Flunisolide 100 mcg twice daily BDP AQ 200 mcg twice daily Study duration: 7 weeks	Run-in: NR Wash-out: NR	NR

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Langrick 1984 England (Fair)	INSS on a 4 pt scale (0=none to 3=severe) recorded daily by the pt and at admission and weeks 3 and 7 by the clinician (INSS: sneezing, stuffy nose, nose blowing, runny nose, post-nasal drip, epistaxis, eye symptoms) Overall efficacy: pt and clinician at each visit Nasal exam at week at admission and wks 3 and 7.	Mean age (years): 66.7 Female gender (%): 37.5 Race not reported	Mean duration of disease (years)=7.3 FN vs BDP Diagnosis, n (%): SAR: 32 (94) vs 28 (80) PAR with seasonal exacerbation: 2 (6) vs 7 (20) asthma: 8 (23.5) vs 11 (31) dermatitis: 4 (11.8) vs 5 (14) Family history of allergies: 12 (35.3) vs 8 (23) Usual severity: Moderate: 15 (44) vs 24 (69) Severe: 19 (56) vs 11 (31)	NR/NR/69	9/6/60 overall efficacy, 66 at wk 3, 51 at wk 7

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Langrick 1984 England (Fair)	FN vs BDP **INSS** FN=BDP (p=NS) for all pt reported INSS. Numbers not given, results only in graphical presentation. **Overall efficacy:** FN(n=28)= BDP (n=32)(p=NS) for any of the responses: Physician, Patient n, (%) Total control: 8 (29) vs 11 (34), 8(29) vs 12 (38) Good control: 18 (64) vs 15 (47), 18(64) vs 18 (56) Minor control: 2 (7) vs 6 (19), 2 (7) vs 2 (6) No Control: No pt reported this outcome

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Langrick 1984 England (Fair)	Elicited by investigator via indirect questioning	FN vs BDP AQ Dry throat of moderate severity: 1 (3) vs 0 Tickling sensation inside of nose: 0 vs 1 (3)	Withdrawals (overall): 9 Withdrawals (adverse events): 0	No SPT for eligibility Other withdrawals were due to non-compliance, pregnancy, lack of treatment effect

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Ratner 1996 USA (Fair)	Double-blind Placebo-controlled Parallel group Multicenter RCT	Adult and adolescent pts with a history of SAR of Mountain Cedar allergy for at least 24 months Positive Skin test to Mountain Cedar Total symptom score at baseline/screening within range of 2 to 7. Stabilized on anti-allergy injection or had not had injection in 1 year proceeding study enrollment Otherwise healthy	FN (old formulation) 100 mcg twice daily FN (new formulation) 100 mcg twice daily Placebo vehicle (new formulation) twice daily Placebo vehicle (old formulation) twice daily Study duration: 6 weeks	Run-in period: NR Wash-out: NR	Chlorpheniramine 4 mg tablets (maximum of 6 tablets per 24 hours)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ratner 1996 USA (Fair)	**INSS**: recorded daily by pt and assessed by the clinician at weekly office visit: Rhinorrhea complex (runny nose, stuffy nose, post-nasal drip), sneezing, nasal itching, and eye symptoms (0-no symptoms to 3-severe symptoms) **TSS**: 4 symptom scores (Rhinorrhea complex, sneezing, nasal itching, and eye symptoms) summed **TNSS**: The scores for rhinorrhea complex, sneezing, and nasal itching were summed	Mean age (years): 44 Female gender: 134 (62%) Race not reported	Baseline TNSS: Numbers not reported but text indicates that there were no differences.	256/NR/218	14/2/136 for efficacy, 216 for safety

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Ratner 1996 USA (Fair)	FN (new) n=34 vs VH (new) n=35 vs FN (old) n=36 vs VH (old) n=31 **INSS (mean score):** **Rhinorrea complex**: 1.64 vs 2.53 vs 1.38 vs 2.36 FN (new) = FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p=0.0003, 0.0001) **Sneezing**: 0.6 vs 1.24 vs 0.64 vs 1.28 FN (new) =FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p<0.0001, <0.0001) **Nasal Itching**: 0.54 vs 1.13 vs 0.53 vs 1.08 FN (new) =FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p=0.0004, 0.001) **Eye symptoms**: 1.02 vs 1.20 vs 1 vs 1.26 FN (new)=FN (old)=VH (new)=VH (old) (p=NS) **Combined Scores on Peak Pollen days (mean score):** **TSS:** 3.81 vs 6.11 vs 3.55 vs 5.97 FN (new) = FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p<0.0001, <0.0001) **TNSS**: 2.79 vs 4.90 vs 2.54 vs 4.73 FN (new) = FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p<0.0001, <0.0001) **Global Assessment:** Would you use this product again? FN (new) n=34) vs VH (new) n=-32 vs FN (old) n=36 vs VH (old) n=29 Yes: 31 (91) vs 21 (66) vs 32 (89) vs 18 (62) No: 3 (9) vs 11 (34) vs 4 (11) vs 11 (38) FN (new) = FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p=0.012, 0.012) Would you prescribe this medication again? FN (new) n=34) vs VH (new) n=-33 vs FN (old) n=36 vs VH (old) n=29 Yes: 31 (91) vs 20 (61) vs 33 (92) vs 16 (55) No: 3 (9) vs 13 (39) vs 3 (9) vs 13 (45) FN (new) = FN (old) (p=NS) Each active drug > VH (old) and VH (new) respectively (p=0.004, <0.001)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Ratner 1996 USA (Fair)	Reported by pt	Rhinitis (34%) and headache (8%) were the most frequently reported drug-related AE, and the most severe. FN (new) vs VH (new) vs FN (old) vs VH (old) **Burning/stinging,** n (%): none: 44 (80) vs 47 (87) vs 32 (58) vs 21 (60) Present: 11 (20) vs 7 (13) vs 23 (42) vs 21 (40) FN (new)>FN(old) (p=0.006) FN (new)=VH (new) (p=NS) FN (old) =VH (old) (p=NS) **Sneezing**, n (%): 2 (4) vs 3 (6) vs 0 vs 1 (2) **Rhinorrhea**, n (%): 4 (7) vs 1 (2) vs 1 (2) vs 0 **Dry nose** n, (%): 2 (4) vs 0 vs 6 (11) vs 1 (2) **Irritation/tenderness**, n (%): 2 (4) vs 3 (6) vs 2 (4) vs 3 (6) **Other**, n (%): 1 (2) vs 4 (7) vs 2 (4) vs 3 (6) **Aftertaste**: none, n (%): 23 (42) vs 34 (63) vs 34 (62) vs 37 (71) less than 10 mins, n (%): 17 (31) vs 13 (24) vs 15 (27) vs 13 (25) 10 mins or more, n (%):15 (27) vs 7 (13) vs 6 (11) vs 2 (4) FN (new) > FN (old) (p=0.006) FN (new) > VH (new) (p=0.005) (FN (old) = VH (old) (p=NS)	Withdrawals (overall):14 Withdrawals (adverse events): 0 One withdrawal was a death from myocardial infarction pt was on FN (old) and his death was deemed unrelated to the study medication. 68 patients excluded due to low pollen count at one center.	68 pt excluded from one center due to low pollen cnt and inability to demonstrate superior efficacy All centers in Texas and pts only SPT for Mountain cedar NS difference for eye symptoms b/n VH and active drug

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Welsh 1987 USA (Fair)	Single-Blind (Cromolyn vs FN) Double-Blind (BDP AQ vs PL) RCT	Adult and adolescent pt with a history of ragweed SAR for 24 mos. (With symptoms in Aug and Sept.) No ragweed hyposensitization for at least 2 years Positive SPT to ragweed Increase in pre-seasonal level of serum IgE antibody to ragweed Patent nasal airway without polyps Not pregnant or lactating Good general health without illness that would interfere with study	DB: BDP AQ 168 mcg twice daily vs PL twice daily SB: FN 100 mcg twice daily vs Cromolyn Sodium 4% 1 spray each nostril four times daily Study duration: 6 weeks Cromolyn and FN (Nasalide) were commercially available. BDP AQ and PL were delivered in metered-dose, manual pump nasal spray containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% (weight/volume) phenylethyl alcohol as vehicle. Beconase AQ consists of a microcrystalline suspension of beclomethasone dipropionate monohydrate in this aqueous medium.	Run-in: Yes x 14 days in which pts recorded symptoms of hay fever/asthma, supplemental antihistamine use, no. of hours spent in air conditioning	supplemental antihistamines, pseudoephedrine (or other equivalents), bronchodilators, theophylline for asthmatic pts

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Welsh 1987 USA (Fair)	**INSS:** Pt kept daily record of symptoms beginning July 11 to Sept 18th. Pt diary included record of time spent in air conditioning as well as use of supplemental antihistamines. **Global assessment** of efficacy by pts at the final visit	Mean age (years): 28 Female gender: 33 (27.5%) Race not reported	Hay fever score (mean out of possible max score of 24): 15.4 Asthma score (mean out of possible max score of 12): 1.89 Pre-seasonal IgEAR (mean ng/mL): 218 Current smokers (mean number of pts): 5 Past ragweed hyposensitization (mean number of pts): 9.5	NR/NR/120	FN vs CR vs BDP AQ vs PL 22/1/ analyzed at baseline: 30 vs 30 vs 29 vs 29 pre-peak: 29 vs 30 vs 28 vs 28 peak: 27 vs 24 vs 27 vs 22 post peak: 23 vs 21 vs 24 vs 22

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Welsh 1987 USA (Fair)	FN vs BDP AQ **Total hay fever scores:** Baseline (FN n=30 vs BDP AQ n=29): 3.8 vs 2.8 Pre-peak (FN n=29 vs BDP AQ n=28): 2.9 vs 2.7 Peak (FN n=27 vs BDP AQ n=27): 4.3 vs 5.5 Post-peak (FN n=23 vs BDP AQ n=24): 3.1 vs 2.8 FN=BDP AQ (p=ns) **Eye symptoms:** FN vs BDP AQ vs PL 8.02 vs 12.63 vs 15.93 (FN=BDP AQ and FN>PL (p<0.05) Mean scores were augmented for use of antihistamines (chlorpheniramine 4 mg and pseudoephedrine 30 mg added a score of 1 and longer-acting medications or larger doses added a score of 2 or 3 accordingly.) **Global assessment of efficacy:** FN=BDP AQ for substantial reduction in hay fever symptoms when compared with previous years.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Welsh 1987 USA (Fair)	Not reported	FN vs CR vs BDP AQ vs PL **Nasal burning:** 10 (33%) vs. 0 vs 0 vs 0 **Sore nose:** 1 (3.3) vs 1 (3.3) BDP AQ 1 (3.3) vs 0 **Headache:** 0 vs 5 (16.7) vs 5 (16.7) vs 1 (3.3) **Nosebleeds:** 0 vs 1 (3.3) vs 0 vs 1 (3.3) **Bad taste:** 0 vs 1 (3.3) vs 1 (3.3) vs 0 **Canker sores:** 1 (3.3) vs 0 vs 0 vs 1 (3.3) **Dry nose:** 1 (3.3) vs 0 vs 0 vs 2 (6.7) **Upper respiratory tract infections** "common cold" during post-peak period: 6 (20) vs 7 (23) vs 15 (50) vs 9 (30)	Withdrawals (overall): 22 Withdrawals (adverse events): 2 (burning and stinging FN)	FN is Nasalide AE 50% common cold with BDP AQ Pollen count included

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Stern 1997 UK, Denmark (Fair)	Placebo-controlled Double-blind (BUD vs PL) Single-blind (BUD vs FP) Multicenter RCT	Adult pts with a history of at least 24 mos. Of SAR provoked by grass pollen Positive SPT or RAST to grass pollen	BUD AQ 64 mcg in one bottle and placebo in the other bottle (one spray in each nostril from each bottle daily=128 mcg once daily) BUD AQ 64 mcg in both bottles (one spray in each nostril from each bottle daily=256 mcg once daily) FP 50 mcg in both bottles (one spray in each nostril from each bottle once daily=200 mcg once daily) Study duration: 4-6 weeks	Run-in: NR Wash-out: NR	terfenadine 60 mg tablets (60-120 mg daily) disodium cromoglycate (20 mg/mL) 1-8 drops to be instilled into each eye daily

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Stern 1997 UK, Denmark (Fair)	**INSS:** daily diary records kept by pts with a 4 pt scale (0=none, 3=severe) Blocked nose, runny nose, sneezing, and eye symptoms **Combined NSS:** Addition of INSS scores **Global assessment of efficacy:** At visit 5 using a 5-pt scale **Safety:** Standard questions from investigators at each visit	Mean age not given Age range: 18-72 Female gender: 266 (44%) Caucasian, n (%) 595 (99) Asian, n (%): 2 (0.33) Black, n (%): 4 (0.66) Other, n (%): 1 (0.1)	Mean disease duration (years): 18.85 Baseline Combined nasal symptoms: PL vs BUD 128 vs BUD 256 vs FP UK/DK: 3.25/1.93 vs 3.24/2.38 vs 2.95/2.25 vs 3.13/2.21	NR/NR/635	84/NR/583 "per protocol analysis" 602 "all pts treated" analysis (out of 602 pt 19 were considered protocol violators and the data was analyzed with and without data from those individuals)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Stern 1997 UK, Denmark (Fair)	INSS PL (n=59) vs BUD 128 (n=181)* vs BUD 256 (n=182) vs FP (n=178) Blocked nose: +0.26 vs -0.35 vs -0.33 vs -0.28 Runny nose: +0.46 vs -0.47 vs -0.46 vs -0.44 Sneezing: +0.31 vs -0.48 vs -0.54 vs -0.45 BUD 256 > FP (p=0.04) Eye symptoms: +0.25 vs -0.02 vs -0.06 vs 0 TNSS (combined nasal symptoms score): +1.02 vs -1.29 vs -1.31 vs -1.18 FP=BUD 128/256 > PL (p<0.001) On days in which pollen cnt > 10 grains/m^3 BUD 256> BUD 128=FP for TNSS (p=0.04), runny nose (p=0.04) and sneezing (p=0.02) *n=180 for blocked nose and combined nasal symptoms Global assessment: PL (n=51) vs BUD 128 (n=177) vs BUD 256 (n=173) vs FP (n=171) Total control of symptoms 31% vs 85% vs 88% vs 82%

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Stern 1997 UK, Denmark (Fair)	Elicited by investigator and reported by pt	33% of individuals reported adverse events during the study. Most frequently reported adverse events were aggravation of asthma (not significantly different between the three treatment groups), followed by flu-like disorder, and headache.	Withdrawals (overall): 84 33 at baseline and 51 during the treatment period Withdrawals (adverse events): 6 (PL=1, BUD 128=1, BUD 256=1, FP=3)	

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Greenbaum 1988 Canada (Fair)	Double-blind Cross-over Multicenter RCT	Adult and adolescent pts with a 12 month history of SAR associated with tree and/or grass pollen Positive SPT to tree and/or grass pollen Sufficiently severe rhinitis to require therapy with NCS (okay if pt had FL (old) in the past)	FN (new) 100 mcg twice daily x 2 weeks FN(old) 100 mcg twice daily x 2 weeks Then cross-over to whichever one pt hadn't used for another 2 weeks	Run-in: NR Wash-out: NR	Chlorpheniramine 4mg tablets If chlorpheniramine was ineffective and/or if side effects occurred with the medication, other marketed antihistamines or decongestants were allowed to be taken concomitantly

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Greenbaum 1988 Canada (Fair)	Pt recorded SE profile daily and reported at 2 and 4 wk visits Pt and investigator subjective evaluation of control of pt's nasal symptoms at 2 and 4 wk visits Pt global assessment of efficacy wk 4	Demographics not reported	24/122 pts had secondary diagnosis of asthma, allergic conjunctivitis, atopic dermatitis Two times as many patients had SAR>5 yrs compared to those who had rhinitis for <5 yrs (numbers not reported) 120/122 pts described their nasal symptoms during the past pollen season as either moderate or severe	NR/NR/122	18/10/ FN(new) (n=110), FN (old) (n=112) for nasal burning/stinging n=110 for throat irritation Overall comparisons of medications (efficacy/safety) (n=107)

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Author Year Country Trial Name (Quality Score)	Outcomes
Greenbaum 1988 Canada (Fair)	Overall comparison of medications: (n=107) Nasal burning and throat irritation: FN (new)<FN (old) (p<0.001 and p=0.009) (less severe SE with New formulation) Overall efficacy: No difference reported between formulations: 58 (54%) Pts who did not perceive a difference in control of nasal symptoms between the two medications: 21 pts preferred FN (old) and 28 pts preferred FN (new) Overall acceptability: 73 pts preferred FN (new), 22 preferred FN (old) (p<0.001) Relief of nasal symptoms reported at the end of each treatment period (2 wks) Pt reported:FN (new)> FN (old) (p=0.43) Investigator evaluation: FN (new) =FN (old) (p=0.399) Antihistamine use (mean number of days used): FN (new)=4.37 FN (old)= 4.39

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Greenbaum 1988 Canada (Fair)	Reported by pt	FN (old) (n=112) vs FN (new) (n=110) **Nasal burning/stinging:** None: 13 (11) vs 52 (47) Just noticeable: 12 (31) vs 36 (33) Mild: 38 (34) vs 15 (14) Moderate: 25 (22) vs 7 (6%) Severe: 15 (13) vs 0 **Throat irritation** (n=110 for both groups): None: 59 (54) vs 65 (59) Just noticeable: 24 (22) vs 26 (24) Mild: 15 (14) vs 11 (10) Moderate: 12 (11) vs 6 (5) Severe: 0 vs 2 (2) **Duration of nasal stinging/burning** (Median) (n=97): FN (new): 0.1 min FN (old): 1 min FN(new)<FN (old) (p<0.001) **Duration of throat irritation** (median) (n=57) FN (new): 1 min FN (old): 0.5 min FN(new)=FN(old) (p=ns) 80 pts reported a difference on duration of nasal burning/stinging between the two products FL (new)<FL (old) (p<0.001) Nausea: < 5% of pts Headache: < 12% of pts	Withdrawals (overall): 18 Withdrawals (adverse events): 8 (5 pt in FN (old), 3 pts FN (new))	Pts didn't record symptom control daily only at the end of each 2 wk treatment period.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Hebert 1996 Canada and Europe (Fair)	Double-blind Parallel group Double-dummy Placebo-controlled Multicenter RCT	Adult pts with history of moderate to severe SAR for at least 24 months Positive skin test to at least one aeroallergen (i.e. tree and/or grass) TSS (nasal and non-nasal symptoms) of at least 6 and INSS scores of at least 2 (moderate severity) for nasal congestion plus one other nasal symptom	MF 100 mcg once daily + PL BDP AQ twice daily and PL MF in the evening MF 200 mcg once daily + PL BDP AQ twice daily and PL MF in the evening BDP AQ 200 mcg twice daily + PL MF twice daily PL BDP AQ and PL MF twice daily (Each pt received a total of 16 sprays per day--double dummy) Treatment duration: 4 weeks	Run-in: No Wash-out: No	Loratadine 10 mg tablets (maximum permitted one tablet per day)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Hebert 1996 Canada and Europe (Fair)	Efficacy and safety assessed at 4,8, 15, 22, and 29 days Rating scale (0=no symptoms to 3=severe symptoms) INSS: pt recorded score in diary twice daily, physician evaluated/scored at each visit TNSS: combined total score of 4 nasal symptoms TSS: combined total score of nasal and non-nasal symptoms Global evaluation of overall efficacy (5-point scale) at each visit by pt and physician(referred to pt diary cards to determine score)	Mean age (years): 32 Female gender (%): 8.5 Race not reported	MF 100 mcg (n=126) vs MF 200 mcg (n=125) vs BDP AQ (n=125) vs PL (n=121) Disease severity (%) Moderate: 72 vs 83 vs 80 vs 77 Severity: 28 vs 17 vs 20 vs 23 Mean TNNS: 8.1 vs 8.1 vs 7.9 vs 8 Mean TSS: 12.7 vs 12.2 vs 12.4 vs 12.8	NR/NR/501	67/NR/497 for safety and 477 for efficacy

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Hebert 1996 Canada and Europe (Fair)	MF 100 mcg vs MF 200 mcg vs BDP AQ vs PL **physician evaluated INSS** (mean percentage change from baseline:) **Rhinorrhea:** Day 4: 32 vs 44 vs 47 vs 30 Day 8: 51 vs 55 vs 58 vs 26 End point: 71 vs 75 vs 73 vs 49 MF 100=MF 200=BDP AQ > PL (for all days except day 4 in which baseline percentage change for MF 100 was not statistically significant when compared with PL) **Nasal stuffiness/congestion:** Day 4: 27 vs 36 vs 43 vs 27 Day 8: 41 vs 35 vs 45 vs 28 End point: 62 vs 67 vs 61 vs 45 MF 100=MF 200=BDP AQ> PL ($p<0.01$ or $p<0.05$) except for MF 100 and MF 200 on Day 4 were not statistically significant when compared to PL **Nasal itching:** Day 4: 35 vs 38 vs 41 vs 23 Day 8: 56 vs 59 vs 58 vs 31 End point: 76 vs 77 vs 74 vs 52 All treatments>PL except MF 100 and 200 at day 4 **Sneezing:** Day 4: 45 vs 49 vs 52 vs 20 Day 8: 63 vs 64 vs 71 vs 32 End point: 80 vs 77 vs 80 vs 58 All treatments>PL ($p<0.01$) at all time points **TNSS physician evaluated** (percentage change from baseline) (estimated from graph:) Day 4:35 vs 43 vs 45 vs 29 Day 8: 53 vs 59 vs 59 vs 34 Day 15: 60 vs 73 vs 64 vs 43 Day 22: 68 vs 85 vs 66 vs 50 Day 29: 78 vs 85 vs 75 vs 59 The only value not statistically superior to placebo was MF 100 at day 4.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Hebert 1996 Canada and Europe (Fair)	Reported by pt and observed by physician	n=497 MF 100 vs MF 200 vs BDP AQ vs PL Any adverse event n, (%): 32 (25) vs 32 (26) vs 38 (30) vs 34 (28) Headache: 10 (8) vs 12 (10) vs 10 (8) vs 8 (7) Epistaxis 4 (3) vs 8 (6) vs 6 (5) vs 4 (3) Nasal burning: 8 (6) vs 4 (3) vs 5 (4) vs 6 (5) Pharyngitis: 4 (3) vs 3 (2) vs 5 (4) vs 5 (4) Sneezing: 3 (2) vs 1 (<1) vs 5 (4) vs 6 (5) AE reported by at least 4% of pts in any treatment group	Withdrawal (overall): 67 Withdrawals (adverse events): 15 (MF 100=4 (3%), MF 200=5 (4%), BDP=0, PL=6 (5%))	0 pts withdrew from BDP AQ grp due to AE Women excluded if of child-bearing age Sprays were given directly after one another (double dummy--16 sprays) MF 100 - diluted by spray of PL would explain day 4 inferiority to MF 200.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Lumry 2003 USA (Fair)	Single-blind parallel group Multicenter RCT	Adult pts with a history of Fall ragweed pollen season during the preceding 24 mos. requiring medication use and were considered candidates for treatment with NCS Positive SPT for ragweed allergen 4 day baseline monitoring of nasal symptoms (discharge, stuffiness, itching, and sneezing) had to be at least 24 out of 48 points	TAA AQ 220 mcg once daily BDP AQ 168 mcg twice daily Treatment duration: 3 weeks	Run-in: No Wash-out: Yes no rhinitis medication was allowed 6 days preceding the baseline visit until the end of the study.	Ophthalmic vasoconstrictor/deconge stant to relieve eye symptoms

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Lumry 2003 USA (Fair)	Efficacy: pt diary card every evening (rating scale 0=none to 3 = severe) evaluating nasal discharge, stuffiness, itching, sneezing, and total eye symptoms (itchiness, tearing, and redness) A nasal index score---combined score of nasal discharge, stuffiness, and sneezing (0-9) Global evaluation of efficacy by pt and physician at final clinic visit. Pt reported SAR (daily comfort scores) every morning RQLQ-prior to treatment, wk 1, 2, and 3 (final visit)	Mean age (years): 37 Female gender (%): 51 White (%): 86.5 Other (%): 13.5	TAA AQ (n=75) vs BDP (n=77) Baseline scores: Nasal stuffiness: 2.5 vs 2.4 Nasal discharge: 2.4 vs 2.4 Sneezing: 2 vs 2.3 Nasal itching: 2.1 vs 2.2 Nasal index: 6.8 vs 7.1 Total eye symptoms: 2 vs 2	NR/NR/152	6/1/147 efficacy at wk 3, 152 for safety, 114 for QOL

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Lumry 2003 USA (Fair)	TAA AQ (n=74 wk 1, 2 and overall, n=72 wk 3) vs BDP AQ (n=77 wk 1, 2 and overall, n=76 wk 2) **Nasal stuffiness:** WK 1: -0.81 vs -0.84 WK 2: -1.05 vs -0.94 WK 3: -1.21 vs -1.09 Overall: -1.01 vs -0.97 **Nasal itching:** WK 1: -0.75 vs -0.90 WK 2: -0.97 vs -1.01 WK -1.21 vs -1.09 Overall: -1.01 vs -0.97 **Nasal discharge:** WK 1: -0.77 vs -0.92 WK 2: -1.04 vs -1.14 WK 3: -1.26 vs -1.27 Overall: -1.01 vs -1.11 **Nasal Index:** WK 1: -2.23 vs -2.76 WK 2: -3.01 vs -3.31 WK 3: -3.63 vs -3.70 Overall: -2.92 vs -3.26 **Sneezing:** WK 1: -0.65 vs -1.01 WK 2: -0.92 vs -1.23 WK 3: -1.15 vs -1.35 Overall: -0.90 vs-1.18 **Total eye symptoms:** WK 1: -0.56 vs -0.53 WK 2: -0.70 vs -0.56 WK 3: -0.86 vs -0.72 Overall: -0.70 vs -0.61 **Global assessment of efficacy:** (numbers not reported) Overall 82.4% of pts and 78.4% of physicians felt that symptoms of rhinitis had greatly or somewhat improved following treatn TAA AQ (n=59) vs BDP (n=55) **RQLQ:** Overall change from baseline: -1.71 vs -1.79 No significant differences between treatments in QOL variables (sleep index, non-hay fever symptoms, practical problems, nasal symptoms, eye symptoms, and activities). **SAR** TAA AQ was statistically significantly preferred (p<0.05) by pt when compared to BDP AQ for both medication odor and taste.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Lumry 2003 USA (Fair)	Reported by pt	TAA AQ (n=75) vs BDP AQ (n=77) Number of pts reporting adverse event, n (%): 26 (35) vs 27 (35) Number of adverse events: 39 vs 34 Body as a whole, n (%) 16 (21) vs 10 (13) Respiratory system, n (%):11 (15) vs 8(10) Skin and appendages, n (%): 1 (1) vs 7(9) Digestive system, n (%): 4 (5) vs 4 (5) Nervous system, n (%): 3 (4) vs 0	Withdrawals (overall): 6 Withdrawals (adverse events): 0	

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Small 1997 Canada (Fair)	Single-blind Parallel group Multicenter RCT	Adult and adolescent pts with a history of Spring SAR for at least 24 months A positive SPT to one or more spring pollen allergens At least 2 or more nasal symptoms including rhinorrhea, congestion, sneezing, and itching upon screening Rhinitis Index score (combined score of the aforementioned symptoms) of at least 24 out of 48 on the 4 highest score of the last 5 days of the drug-free baseline period. Any pt who did not reach the limit of 24 points within 14 days was discontinued from the study.	TAA (aerosol) 220 mcg once daily FP 200 mcg once daily Study duration: 3 weeks	Run-in: No Wash-out: Yes 5-14 days before randomization.	All nonsteroidal medications required by the pt to manage acute or chronic illness unrelated to rhinitis were permitted exception medications that would interfere with the assessment of study drugs.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Small 1997 Canada (Fair)	Pt recorded nasal symptoms (0=none, 3=severe) daily every morning before randomization and throughout the 3 week period Pt rated acceptance on 10 different aspects using a 5 pt scale every day Global assessment of efficacy from Pt and Investigator at wk 1 and 3 (0=no effect on nasal symptoms, 3=AR symptoms and overall discomfort greatly reduced)	Mean age (years): 28 Female gender (%): 52 Race not reported	TAA (n=117) vs FP (n=116) Mean duration of allergy (mo): 162 TAA (n=111) vs FP (n=112) RIS: 7.66 vs 7.9 Congestion: 2.16 vs 2.14 Rhinorrhea: 1.88 vs 2 Sneezing: 1.81 vs 1.78 Nasal itch:1.8 vs 1.76	NR/NR/233	10/0/233 for safety and 223 for efficacy

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Small 1997 Canada (Fair)	TAA (n=111) vs FP (n=112) Mean change from baseline, n (%) **Congestion**: -1.06 (-49) vs -1.19 (-56) (p=0.58) **Rhinorrhea**: -1.1 (-59) vs -1.24 (-62) (p=0.08) **Sneezing**: -1.05 (-58) vs -1.09 (-61) (p=0.51) **Nasal itch**: -0.99 (-55) vs -1.07 (-61) (p=0.64) **RIS**: -4.2 (-55) vs -4.6 (-60) **Global efficacy:** No statistically significant differences between the two treatments for both pt and physician assessments (numbers not reported) **Total daily scores for pt acceptance** (0= not bothersome, 4=bothersome) Medication runs down throat: 0.7 vs 6.77 (p<0.01) Medication runs out of nose: 1.19 vs 6.26 (p<0.01) Medication tastes bad 2.84 vs 5.33 (p=NS) Medication causes sore throat: 1.36 vs 0.77 (p=NS) Medication causes bleeding nose: 0.37 vs 0.14 (p=NS) Medication causes dry nostril: 4.88 vs 2.15 (p<0.01) Medication causes bloody mucus: 0.86 vs 0.65 (p=NS) Medication causes stuff-up nose: 10.67 vs 5.31 (p<0.01)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Small 1997 Canada (Fair)	Reported by pt	TAA (n=117) vs FP (n=116) Overall AE, no pts (%): 31 (26) vs 25 (22) Only reported AE reported by more than 2% of pts Headache, %: 5 vs 9 Epistaxis, %: 3 vs 4	Withdrawals (overall): 10 Withdrawals (adverse events): 1 (TAA group for severe headache)	TAA on market as aerosol using HFA propellant (Nasacort HFA) unclear how to interpret AE for this CFC formulation Pt acceptance scores included due to likeness with AE (eg. Dry nose, sore throat, etc.) Hard to interpret clinically in single blind study.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
LaForce 1994 USA (Fair-good)	Double-blind Placebo-controlled Parallel group Multicenter RCT	Adult and adolescent patients (12-67 years old) with history of SAR for 2 spring seasons A positive SPT to at least one spring allergen present in geographical area Moderate to severe SAR symptoms TNSS of 200/400 on 4 out of 7 days of Run-in	FP 100 mcg twice daily FP 200 mcg once daily BDP AQ 168 mcg twice daily PL twice daily Study duration: 4 weeks	Run-in: yes x 4-14 days Wash-out: No	Chlorpheniramine 4 mg tablets

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
LaForce 1994 USA (Fair-good)	Pt recorded nasal symptoms (0=none, 3=severe) daily every morning (nasal obstruction, rhinorrhea, sneezing and itching) and through-out the entire day x 4 wks Clinician rated nasal symptom severity at weekly clinic visits Global assessment by clinician at end of trial Monitoring of HPA axis function pre-treatment and on the final study day.	Mean age (years): 24 Female gender (%): 29 Race not reported Adolescents (n=110) 10% female Adults (n=128) 45% female (see exclusion criteria)	PL (n=58) vs FP 100 (n=64) vs FP 200 (n=55) vs BDP AQ (n=61) asthma: 22 (38) vs 28(44) vs 29(53) vs 21(34) perennial rhinitis: 41(71) vs 46(72) vs 46(84) vs 46(75) + SPT to grass, n:48 vs 50 vs 44 vs 55 + SPT to tree, n: 40 vs 36 vs 36 vs 30	NR/NR/238	3/0/Number analyzed not totally clear but was either 238 or 235

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
LaForce 1994 USA (Fair-good)	Patient-rated nasal scores FP 100 mcg > BDP AQ in reducing nasal obstruction and rhinorrhea throughout the 4 weeks(p<0.05) Improvement in obstruction, rhinorrhea, sneezing, and itching throughout the trial with FP vs PL Improvement in sneezing and nasal itching throughout the trial with BDP AQ vs PL Rhinorrhea and obstruction (and obstruction upon awakening) were reduced more quickly when compared to BDP and PL. Within the first 12 hours FP 100 mcg had less nasal obstruction than BDP **Overall patient-rated nasal symptoms** for the entire trial: FP 100 mcg >BDP AQ **Overall patient-rated nasal symtpoms** for the second and third weeks: FP 200 mcg>BDP (p<0.05) **Clinician-rated mean total nasal symptoms scores:** Week 1: FP 100 and FP 200 (-0.48) vs BDP AQ (-0.35) Final: decrease with acitve treatements ranged from (-0.55 to -0.67) improvements were significantly greater for the FP 100 mcg group compared with PL (p<0.01) For FP 200 mcg improvements reached significance vs PL only on days 8 and 15. For BDP significantly greater improvements vs PL occured on days 15, 22, and 29 (p<0.05) **Global assessment of efficacy:** FP 100 and 200> PL and BDP >PL (p<or equal to 0.02)

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
LaForce 1994 USA (Fair-good)	Unclear who reported but authors state all events were reported and followed to resolution	PL (n=58) vs FP 100 (n=64) vs FP 200 (n=55) vs BDP AQ (n=61) Any adverse event, n (%): 11(19) vs 8(13) vs 7(13) vs 13(21) Sore throat: 1(2) vs 2 (3) vs 0 vs 2(3) Nasal burning: 2(3) vs 1(2) vs 1(2) vs 4(7) Nosebleed: 2 (3) vs 0 vs 1(2) vs 3(5) Headache: 2(3) vs 3(5) vs 2(4) vs 3(5) HPA monitoring: FP 100 and 200 and BDP: no differences in free cortisol Statistically significant differences in urinary 17-ketogenic steroid levels were observed with FP 100 mcg bid group (9.6 to 11.7 mg) and decreases in the BDP AQ and PL groups (9 to 7.3 mg and 9.4 to 8.6, respectively) For FP 200 mcg--no change (8.5 mg) Authors state not clinically significant and mean values are within normal range.	Withdrawals (overall): 3 Withdrawals (adverse events): 1 (BDP AQ pt with exacerbation of asthma)	110 adults and 128 adolescents AE reported only if more than 3 patients across groups had experienced 10% female in adolescent group Nasal sx recorded throughout entire day ~70% of pts also had perennial rhinitis Raw data in the form of graphs with Y-axis scale such that lines are very close together and meaningful data would be difficult to estimate.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Bronsky 1987 USA (Fair)	Single-blind Multicenter RCT	Adult and adolescent pts Autumn AR x 24 mos (including seasonal exacerbations of perennial rhinitis + SPT to one or more allergens indigenous to the area and season Showed signs of rhinitis > or equal to 8 on EENT evaluation	BDP AQ 84 mcg twice daily BDP AQ 168 mcg twice daily FN (orig. formulation) 100 mcg twice daily FN (orig. formulation) 100 mcg three times daily Study duration: 4 weeks	Run-in:No Wash-out: No	Chlorpheniramine 4 mg tablets

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bronsky 1987 USA (Fair)	Pt recorded nasal symptoms daily (stuffy or runny nose, sneezing or itching, post-nasal drip, puffy itchy or red eyes and sore throat and chlorpheniramine use.) F/U visit (visit 2) 12-16 days after initial visit: EENT repeated by clinician, diary cards collected, AE reported F/U visit (final visit) 26-30 days	Mean age (years): 29 Female gender (%): 52 White n, (%):91 Black n, (%):6 Other n, (%):3	BDP 168 vs BDP 336 vs FN 200 vs FN 300 Mean baseline EENT score: 14.4 vs 15.3 vs 14.2 vs 14	NR/NR/161	NR/NR/Number analyzed not clear because only number of appts totally missed or off-schedule were reported not number of patients

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Bronsky 1987 USA (Fair)	BDP 168 vs BDP 336 vs FN 200 vs FN 300 EENT evaluation scores (0=none, 3=severe) **Changes in mean score after 4 weeks** R**hinitis (physical symptoms)** turbinate swelling: -0.8 vs -1 vs -0.8 vs -0.8 nasal discharge: -0.8 vs -0.1 vs -0.8 vs -0.8 pharyngeal discharge:-0.6 vs -0.6 vs -0.6 vs-0.5 discoloration: -0.9 vs -0.8 vs -0.7 vs -0.7 **Rhinitis-symptoms** sneezing/itching: -1.6* vs -1.4 vs -1.2 vs -1.1* nasal congestion: -1.5 vs -1.4 vs -1.1 vs -1.3 Postnasal drip/snoring: -1 vs -0.7 vs -0.9 vs -0.7 Runny nose/sniffling: -1.3 vs -1.4 vs -1 vs -0.9 *p<0.05; BDP 168 vs FN 200 mcg

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Bronsky 1987 USA (Fair)	Pt reported	BDP 168 vs BDP 336 vs FN 200 vs FN 300 Nasal stinging burning n, (%): 4(10) vs 4(10) vs 12(30) vs 13(33) Headache n, (%): 5(12) vs 4(10) vs 4(10) vs 4(10) Epistaxis n, (%): 3(7) vs 3(8) vs 3(8) vs 3(8) Post-nasal drip n, (%): 1(2) vs 4(10) vs 1(3) vs 3(8) Sore throat n, (%): 0 vs 2(5) vs 3(8) vs 2(5) Nausea n, (%): 0 vs 0 vs 3(8) vs 2(5) Nasal congestion n, (%): 1(2) vs 2(5) vs 1(3) vs 0 Others, n (%): 9 (22) vs 13(33) vs 11(28) vs 6(13)	Withdrawals (overall): NR Withdrawal (due to adverse events): NR	Unclear when pts recorded nasal symptoms No report of attrition Compliance was also recorded in diaries and it is unclear who reviewed the diaries on treatment was three times daily blinding could be broken depending on who is reviewing the diary.

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Meltzer 1999 USA	Double-blind Parallel group Multicenter RCT	Pediatric pts (6 to 11 years of age) Positive SPT or intradermal testing Positive history of SAR (length unspecified) TNS > or equal to 6 out of possible 12 and nasal congestion > or equal to 2 out of 3 at screening and baseline	MF 25 mcg daily MF 100 mcg daily MF 200 mcg daily BDP 84 mcg twice daily Placebo Duration: 4 wks	Run-in: yes (2-7 days) Wash-out: yes (lengths varied depending on medication)	Chlorpheniramine syrup

Abbreviations: (TAA AQ)= triamcinolone acetate aqueous (FP) = fluticasone propionate (RQLQ) = rhinoconjunctivitis Quality of Life Questionnaire (SAQ) = sensory attributes questionnaire (TNSS) = total nasal symptom score (INSS) = Individual nasal symptom score (NR)= not reported (SAR)= seasonal allergic rhinitis (HRQL) = Health- Related Quality of Life (BUD)=Budesonide
(PL0=placebo (FN)=flunisolide, (BDP AQ)=beclomethasone dipropionate aqueous
(MF) = mometasone furoate

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Meltzer 1999 USA	Pt and parents/guardians recorded nasal and non-nasal symptoms in diary twice daily (5 point-scale 1= complete relief to 5=treatment failure) Scores were averaged over day 1 to 15 and 16 to 29 MD completed a physical evaluation days 4 ,8, 15 and 29 and scored nasal and non-nasal symptoms over the past 24 hours and the overall condition of SAR since previous visit (response to treatment compared to baseline)	Mean age (years): 9 Female gender (%):38 White n, (%): 84 Black n, (%): 7 Other n, (%): 9	~70% of pts had PAR ~40% of pts had asthma SAR 5 to 6 years "most patients"	NR/NR/679	33/0/679

Abbreviations: (TAA AQ)= t
(SAQ) = sensory attributes
seasonal allergic rhinitis (H
(PL0=placebo (FN)=flunisc
(MF) = mometasone furoat

Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Outcomes
Meltzer 1999 USA	MF 25 vs MF 100 vs MF 200 vs BDP **TNSS** (MD evaluated-change from baseline estimated from graph): **Day 4**: 2.2 vs 2 vs 2 vs 2.4 **Day 8**: 2.8 for all **Day 15**: 2.9 vs 3 vs 3.1 vs 3.5 **Day 29:** 3 vs 3.7 vs 3.8 vs 3.7 MF 25=MF 100=MF 200=BDP > PL (p </= 0.2) for days 1-15 MF 100=MF 200 >MF 25 and PL days 15-29 **TNSS** (pt evaluated-change from baseline estimated from graph) **Days 1-15:** 1.5 vs 1.9 vs 1.8 vs 1.9 **Days 16-29**: 2 vs 2.7 vs 2.6 vs 2.5 MF 100 and 200=BDP > MF 25=PL MF 200 did not offer any benefit over MF 100 at any time point TSS (nasal and non-nasal-MD evaluated-mean changed from baseline estimated from graph): Day 4: 2.7 vs 3 vs 2.7 vs 3.1 Day 8: 3.7 vs 4.2 vs 3.7 vs 4.2 Day 15: 3.8 vs 4.4 vs 4.1 vs 4.5 Day 29: 4.8 vs 5.5 vs 5 vs 5.2 Endpoint: 4.1 vs 5.5 vs 5 vs 5 MF 100 = BDP > PL on days 4 and 8 MF 100 > MF 25 on Day 29.

Abbreviations: (TAA AQ)= t
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Evidence Table 1. Head-to-head trials in patients with SAR

Author Year Country Trial Name (Quality Score)	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Meltzer 1999 USA	Pt or parent/guardian reported in diary	MF 25 (n=137) vs MF 100 (n=135) vs MF 200 (n=133) vs BDP (n=138) vs PL (n=136) Any adverse event, n (%): 24 (18) vs 27(20) vs 19(14) vs 21(15) vs 31(23) Headache, n (%): 4(3) vs 4 (3) vs 9 (7) vs 8(6) vs 8(6) Epistaxis, n (%): 10 (7) vs 8 (6) vs 3 (2) vs 6 (4) vs 9 (7) Pharyngitis, n (%): 2 (1) vs 1 (1) vs 2 (2) vs 4(3) vs 3 (2) Sneezing, n (%): 6(4) vs 4(3) vs 0 vs 1(1) vs 6(4) Coughing, n (%): 1 (1) vs 2 (1) vs 2 (2) vs 2 (1) vs 1 (1) Nasal irritation, n (%): 0 vs 3 (2) vs 0 vs 0 vs 0	Withdrawals (overall): 33 (5%) Withdrawals (due to adverse events): 14 (2%)	Female pts were pre-menarchal

Abbreviations: (TAA AQ)= t
(SAQ) = sensory attributes
seasonal allergic rhinitis (H
(PL0=placebo (FN)=flunisc
(MF) = mometasone furoat

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Study design, Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Ratner 2006a US	Randomized, parallel, double-blind, placebo-controlled	Age 18-65 yrs; 2-yr history of SAR and experiencing nasal allergy symptoms w/TNSS 8-12 in either morning or evening for at least 3 days during baseline period; demonstrated sensitivity to mountain cedar pollen by positive skin prick test or *in vitro* test specific for IgE; no concurrent disease that could worsen with study participation, not concomitant therapy that could potentially interfere with study.	ciclesonide 25-200 µg/day placebo	1-wk 'baseline period' run-in; inhaled, intranasal or ocular steroids: 30-day washout; oral or topical steroids (other than oral contraceptives and hormone replacement therapy) 42-day washout; oral antihistamines 3 to 10-day washout; intranasal antihistamines 3-day washout; inhaled or oral anticholinergics 12-hour to 7-day washout	Immunotherapy stable for 30 days prior to study entry Chlorpheniramine maleate rescue medication

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ratner 2006a US	Patient-rated 12-hour TNSS assessed 2x/day, day -7 (baseline) to day 14	Mean age: 40 yrs 29% male 95% White 4% Black 1% Asian/other	Previous intranasal corticosteroid use: 49% (355/726)	NR/NR/726	23/NR/726

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse events Reported	Total withdrawals; withdrawals due to adverse events
Ratner 2006a US	Change from baseline in reflective TNSS: C 25 µg/day: -4.8 (p=NS v placebo) C 50 µg/day: -4.8 (p=NS v placebo) C 100 µg/day: -5.3 (p=0.04 v placebo) C 200 µg/day: -5.8 (p=0.003 v placebo) placebo: -4.2 Physician assessed global evaluation of treatment effect at day 14: data not shown; reported as 'somewhat better' than placebo for 100 and 200 µg/day Use of rescue medication: no 'appreciable differences'	Physician assessed incidence of AEs, physical exam, lad values, vital sign monitoring	Pts with at least one AE: C 25 µg/day 36/146 (24.7%) v C 50 µg/day 39/143 (27.3%) v C 100 µg/day 38/245 (26.2%) v C 200 µg/day 32/144 (22.2%) v placebo 31/148 (21.0%) Headache: C 25 µg/day 3/146 (2.1%) v C 50 µg/day 6/143 (4.2%) v C 100 µg/day 2/145 (1.4%) v C 200 µg/day 3/144 (2.1%) v placebo 4/148 (2.7%) Pharyngitis: C 25 µg/day 4/146 (2.7%) v C 50 µg/day 1/143 (0.7%) v C 100 µg/day 5/145 (3.4%) v C 200 µg/day 2/144 (1.4%) v placebo 4/148 (2.7%) Epistaxis: C 25 µg/day 1/146 (0.7%) v C 50 µg/day 3/143 (2.1%) v C 100 µg/day 3/145 (2.1%) v C 200 µg/day 2/144 (1.4%) v placebo 0/148 Nasal passage irritation: C 25 µg/day 0/146 v C 50 µg/day 2/143 (1.4%) v C 100 µg/day 1/145 (0.7%) v C 200 µg/day 3/144 (2.1%) v placebo 2/148 (1.4%) Dizziness: C 25 µg/day 3/146 (2.1%) v C 50 µg/day 0/143 v C 100 µg/day 1/145 (0.7%) v C 200 µg/day 0/144 v placebo 1/148 (0.7%) Intraocular pressure >20mmHg: C 25 µg/day 2/146 (1.4%) v C 50 µg/day 2/143 (1.4%) v C 100 µg/day 2/145 (1.4%) v C 200 µg/day 2/144 (1.4%) v placebo 3/148 (2.0%)	Total withdrawals: 23 (all C doses 17 v placebo 6) Withdrawals due to AEs: 7 (C 5 v placebo 2)

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Study design, Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Ratner 2006b US	Randomized, parallel, double-blind, placebo-controlled	Age ≥12 yrs; good health with a history of SAR requiring treatment; demonstrated sensitivity to mountain cedar pollen (positive skin prick test)	ciclesonide 200 µg/day placebo	7-10 day "baseline period"	Not clearly stated; patients were presumably permitted to continue existing immunotherapy, as text states they were not allowed to increase existing dose of immunotherapy

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Ratner 2006b US	Patient-rated TNSS, assessed morning and evening over 2 wks	Mean age: 40yrs (SD 14) 25% male Ethnicity NR	Average baseline reflective TNSS: 8.9 (SD !.89) Baseline RQLQ score: 3.87 (SD 1.02)	490/NR/327	35/NR/327

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse events Reported	Total withdrawals; withdrawals due to adverse events
Ratner 2006b US	Change from baseline in reflective TNSS at 14 days: C -2.40 (SE 0.16) v placebo -1.50 (SE 0.16); p<0.001 Physician-assessed NS change from baseline at 14 days: C -1.69 (SE 0.15) v placebo -0.92 (SE 0.15); p<0.001 RQLQ score change from baseline at 14 days: C -1.17 (SE 0.10) v placebo).72 (0.10); p=0.002 RQLQ score change from baseline at 28 days (study endpoint): C -1.39 (SE 0.11) v placebo -1.21 (0.11); p=0.244	Physician assessed incidence of AEs, physical exam, lad values, vital sign monitoring	Pts with at least one AE: C 66/164 (40.2%) v placebo 64/163 (39.3%) Headache: C 10/164 (6.1%) v placebo 9/163 (5.5%) Pharyngitis: C 5/164 (3.0%) v 6/163 (3.7%) Epistaxis: C 7/164 (4.3%) v 4/163 (2.5% Upper RTI: C 2/164 (1.2%) v 6/163 (3.7%)	Total withdrawals: 35 (C 21 v placebo 14) Withdrawals dues to AEs: 9 (C 4 vs placebo 5)

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Study design, Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Kaiser 2007 US	Randomized, parallel, double-blind, placebo-controlled	Age >12 yrs with a documented history of SAR caused by ragweed pollen, with SAR symptoms during each of the previous 2 fall allergy seasons, positive skin prick test for ragweed allergen within 12 mos of study entry, moderate to severe nasal and ocular symptoms.	fluticasone furoate 100 μg/day placebo	5-21 day run-in patient-rated symptom scoring	NR

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kaiser 2007 US	Patient-rated 12-hour reflective TNSS, assessed morning and evening and instantaneous TNSS, assessed daily (morning) over 2 wks	Mean age 35 yrs (SD 13.95 yrs) 40% male 90% White 9% Black 2% Other	Mean baseline daily reflective TNSS: 9.8 (SD 1.45) Mean baseline daily reflective ocular symptom score (TOSS): 6.5 (SD 1.45)	428/NR/299	NR/NR/299 (although number withdrawn is not reported, the authors state that 96% of randomized patients completed the study, or ~287 patients)

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse events Reported	Total withdrawals; withdrawals due to adverse events
Kaiser 2007 US	Change from baseline in daily reflective TNSS at day 14: fluticasone furoate -3.55 (SE 0.21) vs placebo -2.07 (SE 0.22) Mean difference: -1.473 (CI -2.01 to -0.94; p<0.001) Change from baseline in daily reflective TOSS at day 14: fluticasone furoate -2.23 (SE 0.16) vs placebo -1.63 (SE 0.17) Mean difference: -0.600 (CI -1.01 to -1.19; p=0.004) Proportion of patients reporting improvement in overall response to therapy: fluticasone furoate 73% vs placebo 52% (p<0.01) Improvement in RQLQ score: no comparative	Clinical and lab testing; patient and physician reports	Pts with at least one AE: fluticasone furoate 31/151 (21%) vs placebo 18/148 (12%) Headache: fluticasone furoate 12/151 (8%) vs placebo 4/148 (3%) Epistaxis: fluticasone furoate 3/151 (2%) vs placebo 1/148 (<1%) Musculoskeletal stiffness: fluticasone furoate 2/151 (1%) vs placebo 1/148 (<1%) Toothache: fluticasone furoate 2/151 (1%) vs placebo 1/148 (<1%) Hypersensitivity: fluticasone furoate 2/151 (1%) vs placebo 0/148	NR

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Study design, Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Martin 2007 US	Randomized, parallel, double-blind, placebo-controlled	Age >12 yrs with a diagonosis of SAR defined by a clinical history of nasal allergy symptoms during each of the two mountain cedar allergy seasons preceding the study, positiv skin prick test to mountain cedar allergen with 12 mos of study entry, adequate exposure to mountain cedar allergen (e.g. residence in a geographical region where exposure was likely to occur)	fluticasone furoate 55-440 µg/day placebo	5-21 day run-in patient-rated symptom scoring	NR

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Martin 2007 US	Patient-rated 12-hour reflective TNSS, assessed morning and evening and instantaneous TNSS, assessed daily (morning) over 2 wks	Mean age 39.3 yrs 34% male 59% White 36% Hispanic 4% Black <1% Asian <1% Other	Duration of SAR: ≥10 yrs 69% of patients 5 to <10 yrs 23% of patients ≥2 to 5 yrs 7% of patients	NR/NR/642	21/3/641 (one post-randomization exclusion)

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse events Reported	Total withdrawals; withdrawals due to adverse events
Martin 2007 US	Change from baseline in daily reflective TNSS at day 14: fluticasone furoate 55µg -3.5 (SE 0.21) fluticasone furoate 110µg -3.84 (SE 0.21) fluticasone furoate 220µg -3.19 (SE 0.21) fluticasone furoate 440µg -4.02 (SE 0.21_ placebo -1.83 (SE 0.21) p<0.001 v placebo for all doses Change from baseline in daily reflective TOSS at day 14: fluticasone furoate 55µg -1.93 (SE 0.17) fluticasone furoate 110µg -2.08 (SE 0.17) fluticasone furoate 220µg -1.92 (SE 0.16) fluticasone furoate 440µg -2.43 (SE 0.17) placebo -1.34 (SE 0.17) p<0.001 v placebo for all doses Proportion of patients reporting improvement in overall response to therapy: fluticasone furoate 55µg 16% fluticasone furoate 110µg 28% fluticasone furoate 220µg 23% fluticasone furoate 440µg 26% placebo 8% p<0.001 v placebo for all doses Improvement in RQLQ score: all fluticasone doses: range -1.79 to -1.97 placebo -0.97; p≤0.006	Clinical and lab testing; patient and physician reports	Pts with at least one AE: fluticasone furoate 55µg 36/127 (28%) fluticasone furoate 110µg 37/127 (29%) fluticasone furoate 220µg 35/129 (27%) fluticasone furoate 440µg 31/130 (24%) placebo 35/128 (27%) Headache: fluticasone furoate 55µg 8/127 (6%) fluticasone furoate 110µg 8/127 (6%) fluticasone furoate 220µg 3/129 (2%) fluticasone furoate 440µg 4/130 (3%) placebo 6/128 (5%) Epistaxis: fluticasone furoate 55µg 4/127 (3%) fluticasone furoate 110µg 10/127 (8%) fluticasone furoate 220µg 12/129 (9%) fluticasone furoate 440µg 9/130 (7%) placebo 5/128 (4%)	21/9

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Study design, Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Fokkens 2007 Europe	Randomized, parallel, double-blind, placebo-controlled	Age ≥12 yrs with a documented history of SAR during each of the two previous grass pollen seasons and either a positive skin prick test or a positive in vitro test within 12 months of study entry.	fluticasone furoate 100µg/day placebo	5-21 day run-in patient-rated symptom scoring	NR

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Fokkens 2007 Europe	Patient-rated 12-hour reflective TNSS, assessed morning and evening and instantaneous TNSS, assessed daily (morning) over 2 wks except for the first day of treatment, when instantaneous TNSS was rated at 4, 6, 8, 10 and 12 hours after theinitial dose	Mean age 30.1 yrs 47% male Ethnicity NR	Duration of SAR: ≥10 yrs 45% of patients 5 to <10 yrs 31% of patients ≥2 to 5 yrs 24% of patients Baseline reflective TNSS: 8.4 Baseline reflective TOSS: 5.4	425/306/285	19/1/285

Evidence Table 1a. Placebo-controlled trials in patients with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse events Reported	Total withdrawals; withdrawals due to adverse events
Fokkens 2007 Europe	Mean change from baseline on reflective TNSS at day 14: fluticasone furoate -4.94 vs placebo -3.18 (LS mean difference -1.757; p<0.001) Mean change from baseline of reflective TOSS at day 14: fluticasone furoate -3.00 vs placebo -2.26 (LS mean difference -0.741 (CI -1.14 to -0.34; p<0.001) Patient response to treatment (significant or moderate improvement): fluticasone furoate 67% vs placebo 39% (p<0.001) Mean change in RQLQ: fluticasone furoate -2.23	AE monitoring, clinical exam, ECG monitoring and laboratory tests	Percentage of patients reporting any AE: fluticasone furoate 24/141 (17%) vs placebo 23/144 (16%) Headache: fluticasone furoate 13/141 (9%) vs placebo 9/144 (6%) Epistaxis: fluticasone furoate 4/141 (3%) vs placebo 1/144 (<1%)	19/2

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Internal Validity

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Berger 2003 USA	Methods not specified	Yes	No, TAA AQ group more severe nasal discharge and stuffiness	Yes	Yes	N/A	N/A single blind	Yes No Yes No
Gross 2002 USA	Methods not specified	Yes	Yes, except Mean age (years): TAA AQ vs FP 40 vs.37.5 (P<0.05)	Yes	Yes	N/A	N/A single blind	Yes No Yes No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

					External Validity	
Author, Year, Country	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-random-ization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Berger 2003 USA	No/NR	No TNSS: unclear, #of pts NR Individual symptom scores: No excluded 5 (1.7%) HRQL: yes	Not reported	Fair	NR/NR/295	Short-or long-acting steroids, a nasal corticosteroid, or nasal cromolyn within 30 days of screening; had taken an antihistamine or leukotriene modifier within 5 days of baseline visit; were pregnant or lactating; had a history of habitual use of nasal decongestants; were hypersensitive or non-responsive to intranasal steroids; had unstable asthma; had begun immunotherapy with 1 month of study initiation; had sinusitis or an underlying nasal pathology resulting in a fixed occlusion of a nostril; showed evidence of a fungal infection of the nose, mouth, or throat; or used TAA AQ of FP within the 3 months before screening.
Gross 2002 USA	No/NR	Not clear, number in each group for efficacy INSS/TNSS per week not reported	No	Fair	NR/NR/352	Short-or long-acting steroids (excluding oral contraceptives and hormone replacement), a nasal corticosteroid, or nasal cromolyn/astemizole within 42 days of screening; were pregnant or lactating; had a history of habitual use of nasal decongestant, were hypersensitive or non-responsive to intranasal steroids; had begun immunotherapy with 1 month of study initiation; disease with the potential to interfere with the evaluation of study medication; use of any medication that might independently affect the symptoms of seasonal AR; an underlying nasal pathology resulting in a fixed occlusion of a nostril; showed evidence of a fungal infection of the nose, mouth, or throat.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Berger 2003 USA	Run-in:No Washout:Yes	No	Yes	Aventis Pharmaceuticals, role not specified	
Gross 2002 USA	Run-in:No Washout:Yes	No	Yes	Aventis Pharmaceuticals, role not specified	

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Ratner 1992 USA	Methods not specified	Not reported	Yes, except P values not reported for Medical history and Perennial rhinitis was FP n=72 (68), BDP n=53 (51), PL n=58 (56)	Yes	Not specifically described, however, medication was dispensed to pts with labels that only indicate for am and pm use	N/A	Yes	Yes No No No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Ratner 1992 USA	No/NR	Numbers of patients in each group are not reported in the results and there is no mention in the text of ITT	No	Fair	NR/NR/NR There were 4 patients that discontinued the study but it is not clear if no. enrolled would then be 317or 313.	Received oral, inhaled, or intranasal steroids within 1 month or intranasal cromolyn within 2 weeks of initiation of the study were excluded

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Ratner 1992 USA	Run-in: Yes Washout: No	No	Yes	Supported by a grant from Glaxo Inc., role not specified	

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Graft 1996 USA	Yes	Not reported	Authors report groups were comparable at baseline. P values not given for demographics number of women at baseline in each group: MF 61/114, BDP 49/112, PL 46/104.	Yes	Yes	NR	Yes	Yes No Yes No
McArthur 1994 UK	Methods not specified	Not reported	Yes, however, they were brief and did not mandate a SPT.	Yes	Described by authors as "single-blind" however, methods of masking treatment were not described	N/A	N/A single blind	Yes No No No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Graft 1996 USA	No/NR	Authors report ITT, however, excluded 2/349 patients who dropped out immediately after randomization and data from 17 patients were invalidated leaving 330 pts available for analysis of efficacy For primary efficacy authors stated that ITT pop showed similar results but did not report numbers	Not reported	Fair	NR/NR/349	Pregnant or breast feeding, receiving immunotherapy (unless receiving a stable dose for at least 2 years with at least moderate symptoms during the last ragweed season); had asthma requiring therapy with inhaled or systemic corticosteroids; were dependent on nasal, oral, or ocular decongestants or antiiflammatory agents; or had rhinitis medicamentosa; multiple drug allergies; a significant medical condition and/or long-term use of medication that might interfere with the study; clinically relevant abnormal laboratory values, vital signs, or electrocardiogram results; and use of any investigational drug within the previous 30 days.
McArthur 1994 UK	No/NR	Authors report ITT, however, for combined mean symptom score n= 77 Global efficacy n=73, AE n=88	No	Fair	NR/NR/88	Two symptoms for entry into the study were not experienced in 1 May to 31 August 1993, had received oral corticosteroids at any time during the 4 weeks before trial entry, had a bacterial, fungal, or viral airway infection, were or intended to become pregnant, had received hyposensitization therapy during the previous 12 months, or had severe asthma.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Graft 1996 USA	Run-in: No Wash-out: yes	No	Yes	Supported by a grant from Schering-Plough Research Institute., Author from this site was included, role not specified	
McArthur 1994 UK	Run-in:No Wash-out: No	No	Yes	Grant from Astra Clinical Research Unit, role not specified	

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Langrick 1984 England	Yes	Not reported	Usual severity of symptoms was greater in the FL group (p=0.004)	Only age and severe hay fever, did not require SPT	Described by authors as "single-blind" however, methods of masking treatment were not described	N/A	N/A single blind	Yes No No No
Ratner 1996 USA	Methods not specified	Not reported	Yes except in height/wt and female gender (62% vs 38%)	Yes	Method of blinding not described	N/A	Methods of blinding not described	Yes No No No
Welsh 1987 USA	Methods not specified	Not reported	Yes	Yes	DB and SB method, however, methods not described	N/A	Yes for BDP AQ and PL, N/A for CR vs FL (single-blind)	Yes No Yes No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Langrick 1984 England	No/NR	No	Not reported	Fair	NR/NR/69	Pregnant or breast feeding, current respiratory tract infection or nasal abnormalities, received systemic steroid therapy within the previous 3 months or anti-allergy treatment within the previous week were not eligible.
Ratner 1996 USA	No/NR	No	Yes 68 pts from one testing center due to low pollen count and inability to show superior efficacy	Fair	256/NR/218	Uncooperative or unable to comply with study requirements, used nasal corticosteroids or nasal cromolyn sodium within 2 weeks of systemic corticosteroids within 4 weeks before randomization, had a total symptom severity score of less than 2 or greater than 7 at randomization visit, were asthmatic and required chronic bronchodilator therapy, or had a history or presence of clinically significant medical disorder that either would have compromised the study results or have been detrimental to the patient
Welsh 1987 USA	No	No	No	Fair	NR/NR/120	Not specifically listed as exclusion criteria, however, pts were included if they did not have nasal polyps, were not pregnant or lactating, had good general health without illness that interfere with the study

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Langrick 1984 England	Run-in: No Wash-out: No	No	Yes	Not reported	Poor**didn't require SPT, single-blind, differences at baseline, not ITT, funding not disclosed
Ratner 1996 USA	Run-in: No Wash-out: No	No	Yes	Grant from Roche Laboratories, role not specified	Pt only in Texas, more female than male, post-randomization exclusion due to low pollen count
Welsh 1987 USA	Run-in: Yes Washout: No	No	Yes	Grant from Glaxo, Inc.	33% female pts age range 12-50

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Stern 1997 UK, Denmark	Methods not specified	Not reported	Yes, however, PL had significantly less pts (n=59) vs (n=181, 182, 180).	Yes	Yes	N/A	Yes when comparing BUD to PL but not BUD to FP	Yes No Yes No
Greenbaum 1988 Canada	Methods not specified	Not reported	Unknown: demographics not given but text indicates the groups are "well balanced"	Yes	DB but methods not specified	N/A	DB but methods not specified	Yes Yes No No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Stern 1997 UK, Denmark	No/NR	Authors report doing an "all patients treated" analysis and stated it was not different from the other analysis. The results were not given as numerical data only description in the text.	No	Fair	NR/NR/635	Had significant symptoms of signs related to the nose other than those of seasonal allergic rhinitis (perennial or atrophic rhinitis), any obstructive structural abnormality in the nose, or nasal polyps. Acute or chronic infectious sinusitis and if they had experienced significant upper respiratory tract infection in the 2 weeks preceding the study. Pts using topical nasal corticosteroid therapy during 1 month before the study or systemic corticosteroids in the 2 months preceding the study were excluded, as were patients who had immunotherapy for seasonal allergic rhinitis in the 2 years preceding the study or astemizole within 2 months of the study.
Greenbaum 1988 Canada	No/NR	No	No	Fair- demographics not given therefore results cannot be reproduced.	NR/NR/122	<12 yo, had known hypersensitivity to corticosteroids, including flunisolide; had active quiescent tuberculosis of the respiratory tract or untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex, or those with unhealed nasal ulcers, surgery or trauma; had any other nasal sinus condition other than SAR; required any concomitant medications in the form of a nasal spray or solution; were pregnant or lactating; or were unable or unwilling to give an informed consent to participate

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Stern 1997 UK, Denmark	Run-in: No Wash-out: No	No	Yes	Grant from Astra Draco AB	
Greenbaum 1988 Canada	Run-in:NR Wash-out: NR	No	Yes	Not clearly reported, however, request for reprints to Author from Syntex, Inc.	Demographics not given

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Hebert 1996	Methods not specified	Not reported	Women 8% Severe disease was slightly higher in MF 100 mcg group at 28% compared to 17-23%	Yes	Yes, DB, double-dummy	N/A	Yes,DB, double-dummy	Yes No No No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Hebert 1996	No/NR	No	No	Fair	NR/NR/501	Asthma requiring therapy with inhaled or systemic corticosteroids, cromoglycate, or nedocromil; were known to be unresponsive to nasal corticosteroids; were dependent on systemic corticosteroids or nasal decongestants; had an allergy to corticosteroids; or had received potent corticosteroid treatment within the last month. Chronic medication or a significant medical condition which could interfere with the study; asthenia or gross obesity; clinically relevant abnormal laboratory tests, vital signs, or electrocardiogram; patients on immunotherapy (unless on a stable regimen for at least 6 mos.); upper respiratory tract infection within the previous 4 weeks; use of any investigational drug within the previous 90 days; nasal polyps or significant nasal structural abnormality; or history of posterior subcapsular cataracts, women who were pregnant, nursing, or at risk of pregnancy (in this study, women requiring birth control or of child-bearing potential) were also excluded. Certain concomitant medications were restricted during the study, including corticosteroids (except for low-potency topical preparations such as hydrocortisone), mast cell stabilizers, antihistamines (apart from rescue loratadine), decongestants, aspirin, nonsteroidal anti-inflammatory drugs, and systemic antibiotics.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Hebert 1996	Run-in:No Wash-out: No	No	Yes	Not specifically stated however one author is associated with Shering-Plough Research Institute	8.5 % female because all women of child-bearing potential were excluded.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Lumry 2003 USA	Methods not specified	Yes	Yes	Yes	Single-blind, however some pts took study drug once daily and others twice daily	N/A	N/A single blind	Yes No Yes No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Lumry 2003 USA	No/NR	No	No	Fair	NR/NR/152	Clinical evidence of any significant physical abnormalities or abnormal laboratory values; nasal candidiasis, acute or chronic sinusitis, significant nasal polyposis or other gross anatomical deformity of the nose sufficient to impair nasal breathing; concurrent medical conditions likely to interfer with the course of the study; use of systemic corticosteroids in the previous 42 days or nasal or inhaled corticosteroids in the previous 30 days; use of nasal cromolyn sodium in the previous 28 days or astemizole in the previous 60 days; treatment with an investigational drug within 60 days; commencement of immunotherapy within the previous six months; use of medication for other medical conditions that might produce or relieve the signs and symptoms of allergic rhinitis for six days prior to and throughout the treatment period; and pregnancy, lactation, or inadequate contraceptive precautions in females of child-bearing potential

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Lumry 2003 USA	Run-in: No Wash-out: Yes x 6 days	No	Yes	Aventis Pharmaceuticals, role not specified	

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
Small 1997 Canada	Methods not specified	Yes	Yes	Yes	Yes	N/A	N/A single blind	Yes No Yes No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
Small 1997 Canada	No/NR	No, efficacy n=223 and safety n=233	No	Fair	NR/NR/233	Women who were pregnant or of childbearing potential and not practiciing approved method of birth control; Pt meeting at least one of the following criteria were excluded: a clinically significant, renal, hepatic, cardiac, respiratory (including asthma), neurologic, collagen-vascular, or psychiatric disorder; cancer; untreated fungal, bacterial, or viral infections; nasal septal ulcer or perforation; nasal surgery or trauma; physical nasal obstruction greater than 50%; a history of habitual abuse of nasal decongestants; use of any systemic, nasal, inhaled corticosteroids within 30 days of screening visit; use of nasal sodium cromoglycate, anticholinergics, vasoconstrictors, or antihistamines (except astemizole) within 7 days of the screening visit; use of astemizole within 60 days of the screening visit; use of topical, oral or both types of decongestants more than three times per week for the previous 3 months(90 days): cardiovascular drugs, hormones, neuroleptics or any other drugs that can cause, suppress, or exacerbate the symptoms of allergic rhinits; immunotherapy unless on a maintenance regimen at the time of screening; history of hypersensitivity or nonresponse to corticosteroids; and participation in another investigational study within 30 days of the screening visit. Steroids were not permitted, except for oral contraceptives and estrogen replacement therapy.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Small 1997 Canada	Run-in: No Wash-out: yes x 5-14 days	No	Yes	Grant from Rhone-Poulene Rorer Canada, Inc. One author from this source as well	Race not reported, M/F equal age range 12-70 Wide variety of allergens due to multicenter, Pollen count not reported. Not ITT, single blind keeps from being rated good

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Randomiz-ation adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contam-ination
LaForce 1994 USA	Methods not specified	Not reported	Yes except for gender, with the placebo group having fewer women	Yes	DB but methods not specified	Not reported	Yes	Yes No Yes No
Bronsky 1987 USA	Methods not specified	Not reported	Yes	Yes	Single-blind, however some pts took study drug twice daily and others three times daily and it is unclear who was collecting the pt diaries	Not reported	N/A single blind	No No Yes No

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-random-ization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria
LaForce 1994 USA	No/NR	Not clear, numbers not reported in results but only 3 out of 238 patients withdrew from study	No	Fair-good	NR/NR/238	Being treated with corticosteroids or intranasal sodium cromolyn, required inhaled or systemic corticosteroid therapy for ongoing asthma, had an upper respiratory tract infection, or if they were scheduled to alter their immunotherapy regimen during the study, women at risk of pregnancy (postmenarchal or premenopausal women and those not using oral contraceptives) and patients with any significant medical disorder or impaired adrenal function as indicated by clinical laboratory tests.
Bronsky 1987 USA	Unknown	Not clear, authors report that of 322 f/u visits 13 were missed completely, 30 were outside the appropriate schedule. No mention of made if this data from these pts was included or exactly how many patients missed appts	No	Fair	NR/NR/161	Pregnancy or lactation, nasal polyps, sinusitis, significant septal deviation, or any other nasal disease; history of alcohol or drug abuse; mental impairment; asthma requiring corticosteroid therapy or sensitivity to inhaled corticosteroid therapy or sensitivity to inhaled corticosteroids; immunotherapy for allergic rhinitis in the month prior to the trial; administration of any investigational drug within 30 days, or corticosteroid or cromolyn sodium within two weeks, or antihistamines within 24 hours prior to the initiation of the trial.

Evidence Table 2. Quality assessment of head-to-head trials in patients with SAR

Author, Year, Country	Run-in/ Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
LaForce 1994 USA	Run-in: Yes Washout: No	No	Yes	Grant from Glaxo, Inc.	
Bronsky 1987 USA	Run-in: No Wash-out: No	No	Yes	Not directly stated but one author is affiliated with Glaxo, Inc.	12-65 yo Multicenter, USA M=F no preg. Or lactating Race included

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Ratner 2006a US	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind	don't know; reported as double blind	no/no/no/no	no

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

				External Validity				
Author, Year, Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**
Ratner 2006a US	yes	no	fair	NR/NR/726	Clinically significcant abnormal lab test results or physical findings of nasal polyps or nasal tract malformations; evidence of ocular herpes simplex or cataracts or history of glaucoma; evidence of a bronchial, pulmonary or RTI or diorders other than AR or asthma w.in 14 days of study; positive test for hep B, hep C or HIV; patients requiring treatment with beta agonists for asthma; patients who took prohibited medications; use of unstable doses of immunotherapy	1 week baseline run-in	no	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Funding	Relevance
Ratner 2006a US	ALTANA Pharma	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Ratner 2006b US	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind	don't know; reported as double blind	no/no/no/no	no

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care
Ratner 2006b US	yes	no	fair	419/NR/327	Nasal pathology including nasal polyps within 60 days of study entry; clinically relevant respiratory tract malformations; recent nasal biopsy; nasal trauma; nasal surgery; atrophic rhinitis; rhinitis medicamentosa; active asthma requiring treatment with inhaled or systemtic corticosteroids; routine use of beta agonists; known hypersensitivity to corticosteroids; history of RTI or disorder within 14 days of screening; treatment with systemic corticosteroids within 2 months of study; treatment with >1% topical steroids within 1 month of study	7-10 day baseline run-in	no	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Funding	Relevance
Ratner 2006b US	ALTANA Pharma	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Kaiser 2007 US	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind	don't know; reported as double blind	no/no/no/no	no

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care
Kaiser 2007 US	yes	no	fair	428/NR/299	Significant concomitant medical condition, including uncontrolled disease of any body system; severe physical nasal obstruction or injury; asthma; rhinitis medicamentosa; bacterial or viral infection within 2 weeks of sudy entry; acute of chronic sinusitis; glaucoma; cataracts; ocular herpes simplex; candida infection of the nose; psychiatric disorder; adrenal insufficiency; use of systemic of inhaled corticosteroid within 8 weeks of study entry; use of inhaled NCS within 4 weeks of study entry; use of other medications that could affect AR or the effectiveness of the study drug	5-21 day baseline run-in	no	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Funding	Relevance
Kaiser 2007 US	GlaxoSmithKline R&D	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Martin 2007 US	method NR	method NR	yes (reported in text only - no table)	yes	don't know; reported as double blind	don't know; reported as double blind	don't know; reported as double blind	no/no/no/no	no
Fokkens 2007 Europe	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind	don't know; reported as double blind	no/no/no/no	no

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/ Washout	Class naïve patients only	Control group standard of care
Martin 2007 US	yes	yes; 1/642	fair	NR/NR/642	Severe physical obstruction of the nose; recent nasal septal surgery or perforation; asthma; rhinitis medicamentosa; upper RTI; chronic use of medications that would affect allergic rhinitis or assessments of efficacy of study medication; current tobacco use; use of subcutaneous omalizumab within 5 months of study; corticosteroids; antihistamines; decongestants; intranasal anticholinergics; oral antileukotrienes within 3 days of study; intranasal or ocular cromolyn within 14 days of study	5-21 day baseline run-in	no	yes
Fokkens 2007 Europe	yes	no	fair	425/NR/285	Severe physical nasal injury or obstruction; asthma; rhinitis medicamentosa; or any other chronic medical condition that could interfere with the course of the study; use of INS within 4 weeks of study; other corticosteroid within 8 weeks; any medication that could affect SAR symptoms or effectiveness of study medication	5-21 day baseline run-in	no	yes

Evidence Table 2a. Quality of placebo-controlled trials in patients with SAR

Author, Year, Country	Funding	Relevance
Martin 2007 US	GlaxoSmithKline	yes
Fokkens 2007 Europe	GlaxoSmithKline	yes

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Kobayashi 1989	Randomized, double-blind, placebo-controlled, parallel Multicenter	Children aged 5-13 years, with seasonal allergic rhinitis Exclusion: Use of systemic corticosteroids, beginning hyposensitization treatment, underlying nasal pathology, history of adverse reactions to inhaled or systematic corticosteroids, concurrent viral infection	beclomethasone dipropionate aqueous nasal spray, 42mcg twice daily vs placebo Study duration: 3 weeks	Decongestants 24 hours before study	Rescue medication: chlorheniramine maleate 4mg
Strem 1978	Randomized, double-blind, placebo-controlled	Children aged 6-15 years with seasonal allergic rhinitis	flunisolide nasal spray, 50mcg three times daily vs placebo Study duration: 4 weeks	NR/NR	NR

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Kobayashi 1989	Evaluated at clinic on study days 4, 8, 15 for nasal and ocular symptoms, Cochron-matel-Haennszel Test, patient daily diary of symptoms	Mean age: 8.8 years 58.4% Male 88.1% Caucasian, 11.8% Other	Mean duration of present episode: BDP-AQ: 9.0 vs placebo: 3.4 No. of seasonal recurrences to date: BDP-AQ: 5.2 vs placebo: 5.3 Previous hyposensitization therapy: BDP: 30 vs placebo: 29	NR/NR/101	0/0/101
Strem 1978	Patient daily diary	Mean age: 10.5 years 70.8% Male Ethnicity NR	NR	NR/NR/48	0/0/48

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Kobayashi 1989	Physician's overall evaluation: Greater improvement with BDP-AQ vs placebo: (p=.012) Improvement at 15 days vs placebo: Nasal obstruction: p= .002 Periocular swelling: p= .007	Patient self-report	Adverse events reported: Bloody nose: BDP: 1 vs placebo: 0 Burning or stinging in nose: BDP: 3 vs placebo: 4 Dizziness: BDP: 1 vs placebo: 0 Drowsiness: BDP: 1 vs placebo: 0 Eye pain: BDP: 0 vs placebo: 1 Headache: BDP: 3 vs placebo: 3	0;0
Strem 1978	Days when symptoms were present >2 hours: Baseline: Sneezing: F: 2.4 vs placebo: 2.5; p=0.89 Stuffy nose: F: 8.0 vs placebo: 7.8; p=0.63 Runny nose: F: 4.4 vs placebo: 3.8; p=0.69 All symptoms combined: F: 9.0 vs placebo: 8.3; p=0.35	Patient self-report	Adverse events reported: flunisolide: moderate: stomatitis, headache, cough, nosebleed, cough mild: sore throat, cough placebo: moderate: sore throat, nausea, cheilosis mild: nosebleed, sore throat, nasal stuffiness	0;0

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Gale 1980	Randomized, double-blind, placebo-controlled, parallel Single-center	Children aged 5-14 years with seasonal allergic rhinitis	flunisolide 50mcg four times daily vs placebo Study duration: 6 weeks	NR/NR	NR
Munk, 1994	Randomized, double-blind, placebo-controlled, parallel Multi-center	Children aged 12-17 years with seasonal allergic rhinitis, naive to intranasal fluticasone propionate, and/or failed therapy with other medications	Intranasal fluticasone propionate 200mcg once daily vs 100mcg twice daily vs placebo Study duration: 2 weeks	NR/NR	chlorpheniramine maleate

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Gale 1980	Patient daily diary	Mean age: 9.7 years 74.2% Male Ethnicity NR	NR	NR/NR/35	NR/NR/NR
Munk, 1994	Clinician and patient symptom scores	Mean age: 14.1 years 93% Male Ethnicity NR	NR	NR/NR/243	3/NR/NR

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Gale 1980	Percentage of patients reported total or substantial control of hay fever symptoms: F: 64% vs placebo: 33%; P<0.05 Improvement of symptoms at 4 weeks: P-values of flunisolide vs placebo: Sneezing: NS Stuffy nose: p< 0.05 Runny nose: p< 0.05	Patient self-report	Number of adverse events reported: At 2 weeks: F: 14 vs placebo: 14 At 4 weeks: F: 6 vs placebo: 9	NR;0
Munk, 1994	Mean rhinitis symptom scores at 15 days: Nasal obstruction: clinician-rated: F100: 39.5 vs F200: 40.8 vs placebo: 54.1 Nasal obstruction: patient-rated: F100: 33.4 vs F200: 38.5 vs placebo: 52.7	Patient self-report	Adverse events reported: Any event: F100: 5 vs F200: 13 vs placebo: 9 Nasal burning: F100: 1 vs F200: 1 vs placebo: 1 Epistaxis: F100: 1 vs F200: 3 vs placebo: 1 Sneezing: F100: 0 vs F200: 1 vs placebo: 3 Urticaria: F100: 1 vs F200: 1 vs placebo: 1	NR;3

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Boner 1995	Double-blind, placebo-controlled, parallel multi-center	Children with seasonal allergic rhinitis for at least one season Exclusion: perennial arthritis, immunotherapy treatment, use of intranasal, inhaled systemic corticosteroids, inhaled, intranasal sodium cromoglycate or neocromil sodium within one month before study	fluticasone propionate aqueous nasal spray 100mcg vs 200mcg vs placebo Study duration: 4 weeks	NR/NR	NR
Schenkel 1997	Randomized, double-blind, placebo-controlled Multicenter	Children aged 6-11 years with spring grass seasonal allergic rhinitis	triamcinolone acetonide aqueous nasal inhaler, 110mcg daily vs 220mcg daily vs placebo Study duration: 2 weeks	NR/NR	NR

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Boner 1995	Physical examination, symptoms assessment	Mean age: 8.3 years Male: 72.6% Ethnicity NR	NR	NR/NR/143	NR/NR/NR
Schenkel 1997	Patient daily diary, 4 clinical visits within 2 week period including physical examination	Mean age: 9 years Male: 65.9% Caucasian: 87%	NR	NR/NR/223	NR/NR/204

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Boner 1995	Median percentage of symptoms-free days: p-value of treatment vs placebo: F100: Sneezing: p=0.016 Rhinorrhoea: p=0.011 Nasal blockage on waking: p=0.011 Nasal blockage during day: p=0.031 F200: Sneezing: p=0.018 Rhinorrhoea: p=0.042	Patient self-report	No. of adverse events: F100: 30 vs F200: 16 vs placebo: 40 No. of patients with adverse events: F100: 20 vs F200: 13 vs placebo: 23 No.of patients with serious adverse events: F100: 1 vs F200: 0 vs placebo: 0 No.of patients withdrawn due to adverse events	NR;2
Schenkel 1997	Mean changes in symptom scores at 2 weeks Nasal Stuffiness: TA110: +0.16 vs TA220: +0.15 vs placebo: +0.15 Nasal Discharge: TA110: +0.15 vs TA220: +0.19 vs placebo: +0.15 Sneezing: TA110: +0.09 vs TA220: +0.22 vs placebo: +0.06	Patient self-report	Percentage of reported adverse events: TA110: 16.2% vs TA220: 23.3% vs placebo: 18.4% Headache reported: TA110: 7% vs TA220: 3% vs placebo: 4% Epistaxis reported: TA110: 1% vs TA220: NR vs placebo: 4%	NR;0

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Banov, 1996	Randomized, double-blind, placebo-controlled, parallel Multicenter	Children aged 6-11 years, with seasonal allergic rhinitis Exclusion: Any clinically relevant deviation from medical lab tests, history of hypersensitivity to corticosteroids, treatment with nasal, inhaled or systemic corticosteroids within 42 days of study	triamcinolone acetonide aerosol nasal inhaler, 220mcg daily, vs placebo Study duration: 2 weeks	NR/NR	NR
Galant, 1994	Randomized, double-blind, placebo-controlled, parallel Multicenter	Children aged 4-11 years, with history of seasonal allergic rhinitis, severe symptoms, and positive skin test reaction to a local autumn allergin	intranasal fluticasone propionate, 100mcg or 200mcg, once daily vs placebo Study duration: 4 weeks	NR/NR	NR

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Banov, 1996	Patient diary symptom scores	Mean age: 9 years Male: 63.7% Caucasian: 93%, African-American: 7%	NR	NR/NR/116	1/0/115
Galant, 1994	Patient diary, analog scales	Mean age: 8 years Male: 64.3% Ethnicity NR	NR	NR/NR/249	7/0/242

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Banov, 1996	Symptom scores at 1 and 2 weeks: Nasal stuffiness: Week 1: TAA: -0.60 vs placebo: -0.33 Week 2: TAA: -0.91 vs placebo: -0.37 Nasal discharge: Week 1: TAA: -0.67 vs placebo: -0.38 Week 2: TAA: -1.02 vs placebo: -0.46	Patient self-report	Adverse events reported: TAA: 31 placebo: 22	1;0
Galant, 1994	Clinician-rated overall response: Better response with both F100 and F200 vs placebo: (p<0.01) Significant improvement: F100: 29% vs F200: 35% vs placebo: 11%	Patient self-report	Adverse events reported: Any event: F100: 4% vs F200: 13% vs placebo: 7% Crusting in nostril: F100: 2% vs F200: 0% vs placebo: 0% Nasal blockage: F100: 0% vs F200: 2% vs placebo: 0% Nasal burning: F100: 0% vs F200: 4% vs placebo: 2%	7;4

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/Washout Period	Allowed other medications/ interventions
Grossman 1993	Randomized, double-blind, placebo-controlled, parallel Multicenter	Children aged 4-11 years, with seasonal allergic rhinitis, positive skin test reaction to late-summer, autumn allergin, moderate to severe nasal symptoms	fluticasone propionate aqueous nasal spray, 100mcg vs 200mcg once daily vs placebo Study duration: 2 weeks	NR/NR	chlorpheniramine maleate

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Grossman 1993	Nasal and ocular symptoms assessed on days 1, 8, 15, 22	Mean age: 8.8 years Male: 65.3% Ethnicity NR	Positive skin test, % Any fall allergin: 100% Weed: 92% Grass: 7.6% Mold: 11.3% History of asthma: 44.6%	NR/NR/250	NR/NR/NR

Evidence Table 3. Placebo-controlled trials in children with SAR

Author Year Country Trial Name	Outcomes	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Grossman 1993	Clinician-rated mean symptom scores at 22 days: Rhinorrhea: F100: 43 vs F200: 46 vs placebo: 48 Sneezing: F100: 22 vs F200: 22 vs placebo: 21 Nasal itching: F100: 33 vs F200: 39 vs placebo: 37 Ocular symptoms: F100: 22 vs F200: 29 vs placebo: 26	Patient self-report	Adverse events reported: Any event: F100: 12% vs F200: 5% vs placebo: 8% Nasal burning: F100: 4% vs F200: 1% vs placebo: 0% Epistaxis: F100: 4% vs F200: 2% vs placebo: 4% Headache: F100: 0% vs F200: 1% vs placebo: 2%	NR;NR

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Banov 1996 US (5 sites)	NR	NR	yes	yes	NR	NR	NR	yes	none
Boner 1995 Europe (18 sites, specific countries not listed)	NR	NR	yes	yes	NR	NR	NR	yes	none
Galant 1994 US (10 sites) same data reported in Anonymous, 1994 and Grossman, 1993	NR	NR	yes	yes	NR	NR	yes	yes	none

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

				External Validity	
Author, Year, Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Banov 1996 US (5 sites)	no - 1 patient ran out of medication prior to end of treatment period, 2 patients did not have usable data	NR	fair	NR/ NR/ 116	Any clinically relevant deviation from normal medical or laboratory values, existing nasal candidiasis or acute sinusitis, history of hypersensitivity to corticosteroids, treatment with nasal, inhaled or systemic corticosteroids within 42 days of study initiation, treatment with nasal cromolyn sodium within 14 days of study initiation, use of any investigational drug within 90 days, use of any medication that could effect signs/symptoms of allergic rhinitis, immunotherapy within 30 days of enrollment, previous participation in TAA aerosol nasal inhaler study
Boner 1995 Europe (18 sites, specific countries not listed)	yes	NR	fair	NR/ NR/ 143	Perennial rhinitis, immunotherapy (time frame not specified), use of intranasal, inhaled or systemic corticosteroids within 1 mo of study, use of intranasal or inhaled sodium cromoglycate or nedocromil sodium within 1 mo of study, use of astemizole within 6 wks of study
Galant 1994 US (10 sites) same data reported in Anonymous, 1994 and Grossman, 1993	no - 7 withdrawals (4 unrelated AEs, 2 protocol violations, 1 consent withdrawal)	NR	poor	NR/ NR/ 249	Exposure to intranasal, inhaled or systemic corticosteroids within 1 mo of enrollment, or within 3 mos of enrollment for patients requiring the equivalent of prednisone 20mg/day > 2 mos), intranasal cromolyn sodium therapy within 2 wks of enrollment, nasal symptom score of at least 200 pts (self reported) for at least 4 of 7 days preceding entry into study

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Author, Year, Country	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Banov 1996 US (5 sites)	NR	NR	yes	Rhone-Poulemc Rorer	yes
Boner 1995 Europe (18 sites, specific countries not listed)	run-in not reported/ 2 wk washout	NR	yes	NR	yes
Galant 1994 US (10 sites) same data reported in Anonymous, 1994 and Grossman, 1993	4-14 day run-in/ washout not reported	NR	NR	Glaxo	yes

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Gale 1980 Australia	NR	NR	yes	yes	NR	NR	yes	yes	none
Kobayashi 1989 US (2 sites)	unclear - "random code" was used	NR	yes	yes	NR	NR	NR	NR	none
Munk 1994 US (12 sites)	NR	NR	yes	yes	NR	NR	NR	NR	none

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

				External Validity	
Author, Year, Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Gale 1980 Australia	yes	NR	fair	NR/ NR/ 35	Allergen injections for at least 2 yrs, underlying symptoms of nasal pathology, use of medications which could potentially mask symptoms of allergic rhinitis or affect adrenocorticol function
Kobayashi 1989 US (2 sites)	no withdrawals	NR	fair	NR/ NR/ 101	Use of systemic corticosteroids, beginning hyposensitization treatment, underlying nasal pathology, history of adverse reactions to inhaled or systemic corticosteroids, concurrent viral or bacterial infection
Munk 1994 US (12 sites)	yes for safety, unclear for efficacy	NR	fair	NR/ NR/ 243	Use of intranasal cromolyn sodium 2 wks preceding study, use of intranasal, inhaled or systemic steroids for 1 mo prior to enrollment

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Author, Year, Country	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Gale 1980 Australia	2 wk run-in*/washout not reported (*text indicates "2-week pretreatment baseline period...followed by a 4-week treatment period" however accompanying table appears to indicate that medication was given during the 2 wk baseline period)	NR	yes	NR	yes
Kobayashi 1989 US (2 sites)	1 wk run-in, no allergic rhinitis medications, 24 hr run-in no decongestants/ washout not reported	NR	yes	NR	yes
Munk 1994 US (12 sites)	4-14 day run-in, chlorpheniramine maleate 4mg allowed as rescue during run-in/washout not reported	no	yes	NR	yes - study population 12-17 yrs

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high
Schenkel 1997 US (number of sites unclear)	NR	NR	yes	yes	NR	NR	NR	NR	none
Strem 1978 US	NR	NR	no; runny nose significantly more severe in the flunisolide group	yes	NR	NR	NR	NR	none

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

				External Validity	
Author, Year, Country	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**
Schenkel 1997 US (number of sites unclear)	yes for safety, unclear for efficacy	NR	fair	NR/ NR/ 223	Any medical conditions that might interfere with the study significantly, clinically relevant deviations from normal medical or laboratory parameters, nasal candidiasis, acute or chronic sinusitis, significant nasal polyposis or other gross nasal deformity sufficient to impairing nasal breathing, use of systemic corticosteroids within 42 days, use of nasal cromolyn sodium within 28 days, use of nasal or inhaled corticosteroids within 30 days, astemizole within 60 days, immunotherapy within 6 mos, use of investigational drug within 90 days
Strem 1978 US	yes	NR	fair	NR/ NR/ 48	NR

Evidence Table 4. Quality assessment of placebo-controlled trials in children with SAR

Author, Year, Country	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Schenkel 1997 US (number of sites unclear)	6 day run-in, no rhinitis relief medications; washout not reported	no	yes	Rhone-Poulemc Rorer	yes
Strem 1978 US	2 wk run-in/washout not reported	NR	yes	NR	yes

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Fair quality studies				
Drouin 1996 Europe/Canada (Fair)	RCT, double-blind, parallel, multicenter	Aged ≥ 12 years; ≥ 2 year history of moderate-severe PAR warranting chronic use of intranasal corticoids for symptom control; active disease at both screening and baseline; positive skin test to ≥ 1 perennial allergen of continuous exposure within last two years; wheals induced by skin prick or intradermal injection must have been ≥ 3 mm or ≥ 7 mm, respectively, larger than diluent control	Mometasone QD (200 µg) Beclomethasone BID (400 µg) Placebo x 12 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Fair quality studies						
Drouin 1996 Europe/Canada (Fair)	Rescue medication=loratadine 10 mg QD PRN	**Primary outcome:** average change from baseline in total AM + PM diary nasal symptom score (sum of scores for rhinorrhea, congestions, sneezing, and nasal itching; each rated on 4-point scale of 0=none to 3=severe) over the first 15 days of treatment for comparison of mometasone vs placebo **Secondary:** total diary nasal symptom scores averaged over 15-day intervals behond day 15; all other composite total and individual diary symptom scores, physician-evaluated perennial rhinitis symptoms, as well as physician and patient evaluations of therapeutic response Assessments conducted at research center visits at weeks 1, 2, 4, 8 and 12; ratings based on patient diary assessments and physician ratings	31.7 years 45.4% Race NR	Mean duration of condition (yrs): 11.3 With asthma (% pts): 20.4 With SAR (% pts): 48.9	NR/NR/427	100 (23.4%) withdrawn/14 (3.3%) lost to follow-up/387 analyzed Mometasone n=129 vs beclomethasone n=134 vs placebo n=124

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Fair quality studies			
Drouin 1996 Europe/Canada (Fair)	mometasone vs beclomethasone (data NR; estimated from figure) Average change from baseline in total AM+PM nasal symptoms (patient diary): Days 1-15 (primary outcome): -25% vs -29%; NS Endpoint: -46% vs -51%, NS Average change from baseline in physician-rated individual and total nasal symptom scores (range): -34% to -58% vs -40% vs -64%, NS % patients demonstrating complete or marked symptom relief (week 12): 54% vs 53% loratadine use (% patients): 48% vs 46%, NS	Adverse events were solicited at each treatment visit and the date, time of onset, and duration were recorded; severity of each adverse event was defined as mild, moderate, or severe; investigator assigned each adverse event as unrelated, possibly, probably or related	% patients with (all p=NS): Any treatment-related adverse event=43% vs 42% Epistaxis/blood in nasal discharge: 27 (19%) vs 34 (23%) Headache=14(10%) vs 10(7%) Pharyngitis=6(4%) 9(6%) Coughing=4(3%) vs 4 (3%) Rhinitis=1(<1) vs 4(3%) Nasal irritation=4(3%) vs 5(3%) Nasal Burning=4(3%) vs 4(3%) Sneezing=1(<1%) vs 4(3%) Infection, viral 0 vs 1(<1%) Pruritus: 0 vs 0

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Fair quality studies		
Drouin 1996 Europe/Canada (Fair)	% patients with: Withdrawals due to adverse events=8(5.6%) vs 6(4.1%), NS Total withdrawals: 32 (22.4%) vs 29 (19.9%), NS	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Meltzer 2005 US	RCT, double-blind, cross-over, multicenter	aged 18-65 years, symptomatic for allergic rhinitis with a total nasal symptom severity score less than/equal to 6 and more than/equal to 2 (nasal congestion, rhinorrhea, sneezing and pruritis). All individuals needed to be in good health and free of any clinically significant disease other than allergic rhinitis	Mometasone (200 µg) one time dose Fluticasone (200 µg) one time dose 30 minutes between drug application	10 minutes before receiving each drug, study participants cleansed their mouth with one unsalted cracker and several swallows of water and cleanse the nose by sinffing a swatch of wool

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Meltzer 2005 US	none that would mask the symptoms of rhinitis or any investigational drugs	primary outcome:from the product attribute questionnaire immediately scent or odor immediate taste bitter taste run down throat run out of nose feel soothing induce urgency to sneeze after 2 min. scent or odor bitter taste run down throat run out of nose feel soothing aftertaste cause nasal irritation how bothersome was nasal irritation secondary outcome: overall preference questionnaire	38.7 year 67% 77% white	mean duration of allergic rhinitis history: 21.5 months	NR/NR/100	0/0/100

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Meltzer 2005 US	Mometasone vs. fluticasone primary outcome:from the product attribute questionnaire, mean rating immediately scent or odor: 0.6 vs.3.0, p<0.0001 immediate taste: 0.5 vs 1.1, p=0.0002 bitter taste: 0.5 vs 0.7, p=0.24 run down throat: 1.0 vs. 1.1, p=0.78 run out of nose: 0.7 vs. 1.1, p<0.05 feel soothing: 2.5 vs. 2.0, p=0.03 induce urgency to sneeze: 0.5 vs. 0.6, p=0.63 after 2 min. scent or odor: 0.4 vs. 2.45, p<0.0001 bitter taste: 0.4 vs. 0.4, p=1.00 run down throat: 1.2 vs. 1.3, p=0.81 run out of nose: 0.75 vs. 1.0, p=0.08 feel soothing: 1.9 vs. 2.0, p=0.49 aftertaste: 0.6 vs. 1.0, p=0.007 cause nasal irritation: 0.7 vs. 0.75, p=0.82 how bothersome was nasal irritation: 0.75 vs. 0.8, p=0.72	NR	NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Meltzer 2005 US	0/None	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Richards 1996(b)	Double-blind, placebo-controlled Multi-center	Children aged 4-11, with perennial arthritis	fluticasone propionate 100mcg once daily vs 200mcg twice daily vs placebo Study duration: 4 weeks	NR/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Richards 1996(b)	Antihistamines not permitted 48 hours before study. Rescue anti-histamine provided (drug NR)	Patient daily diary of symptoms, investigator assessments every 2 weeks of symptoms, nasal condition, haematology testing, plasma cortisol levels	Mean age: 8.83 years Male: 74% Ethnicity: Caucasian: 88%; Asian: 6.3%; Other: 5.6%	Perennial allergic arthritis: 66.3% Perennial nonallergic rhinitis: 28.6%	NR/NR/415	NR/NR/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Richards 1996(b)	Percentage of patients with reduction of rhinorrhea with FPANS, after reporting moderate/severe symptoms at baseline: 60% reporting no/mild symptoms at 4 weeks Increase of symptom-free days, vs placebo: FPANS: p=0.05 vs BDPANS: p=0.03	Patient self-report	Adverse events reported: Any event: FPANS: 48% vs BDPANS: 67% vs placebo: 40% Upper respiratory tract infection: FPANS: 12% vs BDPANS: 20% vs placebo: 8% Headache: FPANS: 6% vs BDPANS: 13% vs placebo: 4% Cough: FPANS: 6% vs BDPANS: 13% vs placebo: 4%

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Richards 1996(b)	0;9	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Bachert 2002 Norway, Germany, Switzerland (fair)	Randomized double-blind (patient) single dose, crossover single center	Adults (18-70y) with at least a 2 year history of allergic rhinitis (seasonal or perennial), who were symptomatic at baseline with a positive response to skin prick test for at least one allergen prevalent in the geographic area Exclusion: received intranasal coorticosteroids within 1 weekof randomization, systemic or topical antihistamines, chromones or leukotriene modifiers within 48h of randomization, an investigational drug within 30d of randomization or depot corticosteroids within 8 weeks of randomization, presence of nasal candidiasis, herpes lesions, acute or chronic sinusitis, severe impairment of nasal breathing, clinically relevant deviations from normal in the general physical examination and pregnant or lactating women.	triamcinolone acetonde aqueous 220mcg vs Fluticasone proprionate aqueous, 200mcg vs. Mometasone furoate aqueous 200mcg Study period: 1 day	Washout before each treatment administration with unsalted crackers, rinse with water and sniff a swatch of wool. Washout period:30 min. between medications

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bachert 2002 Norway, Germany, Switzerland (fair)	NR	Adjusted scores of Nasal Spray Evaluation Questionnaire recorded by a trained interviewer (scale of 0-100) immediately after treatment: Overall comfort, Amount of medication runoff, Amount of irritation, strength of urge to sneeze, Stength of odor, Strength of taste, Bitter taste, Moist nose and throat after 2-5 minutes: Strength of aftertaste, Amount of irritation, Amount of medication runoff	33.5 years 47% female White: 96%, other: 4%	Perennial allergic rhinitis: 13% Seasonal allergic rhinitis: 48% Both: 39% Diagnostic test: skin prick 73%, RAST 24%, none 3% main symptoms: nasal discharge 63%, itchy nose 46%, sneezing 62%, nasal congestion 74% prior medications: antihistamine 42%, nasal corticosteroid 40%, cromone 14%, antileukeotriene 14%, at least one 79% concomitant medications: antileukotriene 7%, bronchodilator 5%, inhaledcorticosteroid 3%, at least one 39%	NR/NR/109	14/0/95

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Bachert 2002 Norway, Germany, Switzerland (fair)	Adjusted scores of Nasal Spray Evaluation Questionnaire recorded by a trained interviewer Estimated from graph, not directly reported, p-values as reported below: * significant for TAA vs MF, # significant for TAA vs FP, ++ significant for FP vs MF immediately after treatment: Overall comfort: 65 vs 63 vs 59, * # Run down throat and nose: 32 vs 24 vs 23, * # Amount of irritation: 15 vs 16 vs 23, * ++ Strength of urge to sneeze:5 vs 5 vs 5, NS Stength of odor: 17 vs 63 vs 59, * # Strength of taste: 15 vs 20 vs 24, * # Bitter taste: 9 vs 10 vs 13, NS Moist nose and throat: 60 vs. 53.5 vs. 53, * # after 2-5 minutes: Strength of aftertaste: 10 vs 18 vs 18.5, * # Amount of irritation: 10 vs 16 vs 19, * # Amount of medication runoff: 20 vs 18 vs 19, NS	NR	1 patient with mild dizziness possibly drug-related with Mometasone. NSD between treatments, no serious adverse events

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Bachert 2002 Norway, Germany, Switzerland (fair)	14; 0	This seems to be the same data reported in the Stokes 2004 pooled analysis Study B

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Shah 2003 USA (fair)	Randomized single-blind (patient) single dose, crossover single center USA	Adults >18y with > 1y history of allergic rhinitis (seasonal or perennial), experiencing mild to moderate symptoms of allergic rhinitis as determined by 24h reflective total nasal symptom score on the study day. Also all patients had a history of either inadequate control of symptoms with antihistamines, decongestants, and /or immunotherapy, or previous success with intranasal corticosteroids other than budesonide or fluticasone, treatment naive for two study medications Exclusion: pregnancy, nursing, or not using accepted method of birth control presence of nasal candidiasis, rhinitis medicamentosa, atrophic rhinitis, acute of chronic rhinitis and nasal obstructions or abnormalities significant disease history or unstable medical condition, use of topical nasal corticosteroid treatment within 2 wks before study, history of hypersensitivity or intolerance to corticosteroids, use of medications that could mask symptoms of rhinitis immediately after study treatment day, use of an experimental drug within 30 days preceding study initiation, previous use of study medications	Single dose of 64mcg budesonide aqueous and 200mcg fluticasone proprionate with washout period or single single dose of 64mcg budesonide aqueous and 100mcg fluticasone proprionate with washout period	Washout before study begin with small cup of water, crackers and swatch of wool. Washout period: 1 hr. between medications in Study I and 2 hrs. between medications in Study II

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Shah 2003 USA (fair)	NR	Sensory Perceptions Questionnaire: Patients rated their sensory perceptions and the degree of their perceptions using Likert Scales	Study I: Mean age 40y, Range 18-73y, 60.8% women, 39.2% men, 69.1% white, 16% Black, 11.6% Hispanic, 3.3% Asian, 0% other Study II: Mean age 38y, Range 18-80y, 71.6% women, 28.4% men, 75.8% white, 4.2% Black, 17.4% Hispanic, 1.1% Asian, 1.6% other	Study I vs. Study II: Baseline total nasal symptom score: Mean 7 vs. 7, Range 3-12 vs. 4-11 Allergic rhinitis duration (y): Seasonal and perennial, Mean 19 vs. 18, Range 1-58 vs. 1-62 Perennial, Mean 16 vs. 13, Range 3-49 vs. 2-30 Seasonal, Mean 14 vs. 18, Range 1-47 vs. 1-50	NR/NR/n=181 in Study I and n=190 in Study II	Study I: 1/1/179-181 Study II: 0/0/187-190

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Shah 2003 USA (fair)	Percentage of patients responding yes when asked if they perceived specific sensory attributes Estimates from graph *p<0.001; # p<0.019 Study I (Fluticasone 200mcg vs. beclomethasone 64mcg) Scent: 79% vs 34%* Taste: 39% vs 15%* Aftertaste: 37% vs 15%* Throat Rundown: 46% vs 25%* Nose Runout: 48% vs. 40% # Study II (Fluticasone 100mcg vs. beclomethasone 64mcg) Scent: 91% vs 30%* Taste: 34% vs 15%* Aftertaste: 33% vs 23%, NS Throat Rundown: 40% vs 32%, NS Nose Runout: 42% vs. 36%, NS	Patient report	Adverse events were not reported separately by treatment group, only by study I and II. Study I: 9 patients (5%) any-cause adverse event, 0 treatment-related Study II: 11 patients (5.8%) any-cause adverse event, 7 treatment-related rhinitis (n=4), dry mouth (n=1), nausea (n=1), headache (n=1) No serious adverse events reported in either study

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Shah 2003 USA (fair)	1/ 0 in Study I 0/ 0 in Study II	Study was designed to evaluate patients perceptions and preference for specific sensory attributes of medications

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Stokes 2004 USA, Norway, Germany, Switzerland (fair-poor)	Randomized double-blinded crossover 2 multicenter	Adults (18-70y) with at least a 2 year history of allergic rhinitis (seasonal or perennial), who were symptomatic at baseline with a positive response to skin prick test for at least one allergen prevalent in the geographic area Exclusion: received intranasal corticosteroids within 1 weekof randomization, systemic or topical antihistamines, chromones or leukotriene modifiers within 48h of randomization, an investigational drug within 30d of randomization or depot corticosteroids within 8 weeks of randomization, presence of nasal candidiasis, herpes lesions, acute or chronic sinusitis, severe impairment of nasal breathing, clinically relevant deviations from normal in the general physical examination and pregnant or lactating women	triamcinolone acetonde aqueous 220mcg vs Fluticasone proprionate aqueous, 200mcg vs. Mometasone furoate aqueous 200mcg Study period: 1 day	Washout before each treatment administration with unsalted crackers, rinse with water and sniff a swatch of wool. Washout period:30 min. between medications

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Stokes 2004 USA, Norway, Germany, Switzerland (fair-poor)	NR	Adjusted scores of Nasal Spray Evaluation Questionnaire recorded by a trained interviewer (scale of 0-100) Immediately after treatment: Overall comfort, Amount of medication runoff, Amount of irritation, strength of urge to sneeze, Stength of odor, Strength of taste, Bitter taste, Moist nose and throat after 2-5 minutes: Strength of aftertaste, Amount of irritation, Amount of medication runoff	36.2 years 54.4% female Caucasian 92.6%, black 4.2%, Asian 1.9%, Hispanic 1.4%, Other 0.0	NR	NR/NR/215	NR/NR/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Stokes 2004 USA, Norway, Germany, Switzerland (fair-poor)	Adjusted scores of Nasal Spray Evaluation Questionnaire recorded by a trained interviewer immediately after treatment: Overall comfort: 70.4 vs 70 vs 65, p=0.004 Amount of medication runoff: 28.1 vs 25.1 vs 27.4, p=0.289 Amount of irritation: 16.1 vs 16.8 vs 22.4, p=0.003 strength of urge to sneeze: 8.9 vs 9.3 vs 11.5, p=0.190 Stength of odor: 14.8 vs 54.3 vs 53.2, p<0.001 Strength of taste: 14.3 vs 20.5 vs 26.1, p<0.001 Bitter taste: 8.1 vs 9.2 vs 13.7, p=0.003 Moist nose and throat: 60.0 vs. 55.8 vs. 55.8, p=0.011 after 2-5 minutes: Strength of aftertaste: 12.8 vs 18.9 vs 21.1, p<0.001 Amount of irritation: 14.5 vs 16.3 vs 21.3, p<0.001 Amount of medication runoff: 20 vs 18 vs 19, NS	NR	NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Stokes 2004 USA, Norway, Germany, Switzerland (fair-poor)	NR	Pooled analysis of two separate trials. Study B has significantly younger ($p<0.05$) and higher percentage of Caucasians ($p<0.01$) than Study A

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Bunnag 2003 Asia (fair)	Randomized double-blinded crossover multicenter	Adults >18y with a 2y history of allergic rhinitis, positive skin prick test and/or positive RAST w/i 2 y to at least one allergen prevalent in the geographic area to which they had continuous exposure Exclusion: use of intranasal medications in the 48h preceding the first assessment, oral or systemic corticosteroids in the 2 wks.preceding the first assessment, or depot corticosteroids in the 2 wks.preceding the first assessment, topical decongestants, topical antihistamines and topical cromoglycates prior to the study, previous history of nasal surgery, nasal or paranasal sinus diseases, severe deviated nasal septm or abnormal sense of smell or odor sensation and illiterate patients	fluticasone proprionate aqueous, 200mcg vs. mometasone furoate aqueous 200mcg vs. triamcinolone acetonde aqueous 220mcg	Washout before study begin with small cup of water and crackers. Washout period: 30 min. between medications

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bunnag 2003 Asia (fair)	NR	Patients responded to questions given by a trained, independent, blinded interviewer after administration of each of the products. Patients rated drugs using a 100-point scale immediately for comfort of use, amount of medicine that ran down throat from the nose, irritation, sneezing, strength of odor, liking of odor, strength of taste, liking of taste, and dry or moist sensation of nose and throat. After 2 minutes, patients rated: strength of aftertaste, irritation, amount of medicine taht ran down throat from nose, and overall liking	Mean age 30.5y, age range 18-72 54.4% female, 45.6% male Indonesia 32.9%, Singapore 31.6% and Thailand 35.4%	NR	NR/NR/364	3/NR/361

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Bunnag 2003 Asia (fair)	Sensory Perception attribute ratings-upon adminstration: Comfort 55.9 (24.0) vs 53.5(23.9) vs 58.2(26.5) p=0.0406 Medicine ran down throat 17.5(25.4) vs 16.8(23.9) vs 15.4(23.2) NS Irritation 23.8(26.7) vs 25.5(27.9) vs 22.9(28.6) NS Sneeze urge 13.1(25.9) vs 12.5(23.7) vs 13.6(26.5) NS Strength of Odor 52.8(24.1) vs 52.7(24.5) vs 37.4(23.9) p<0.0001(chi-square test) Strength of taste 37.0 (23.3) vs 40.4(27.2 vs 31.8(20.8) NS Dry/Moist 46.9(28.5) vs 46.8(29.1) vs 45.8(29.7) NS after 2 minutes Aftertaste 35.2%yes vs 34% yes vs 30.7% yes NS Strength of aftertaste 39.6 (24.4) vs 37.9(25.2) vs 34.3(24.2) NS Irritation 17.1(23.8) vs 19.6(24.7) vs 17.3(25.0) NS Medicine ran down throat 21.6(26.5) vs 19.5(24.6) vs 19.8(25.2) NS	Adverse events reported were reported spontaneously by the patients or observed by the investigated/interviewer and were recorded on the case report form after each nasal spray administration	None reported

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Bunnag 2003 Asia (fair)	3/NR	Study was designed to evaluate medication preference, sensory perceptions and compliance

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Mandl 1997 Europe, Latin America and Canada (Fair)	RCT, double-blind (double dummy), parallel, multicenter	Aged ≥ 12 years; ≥ 2 year history of moderate-severe PAR warranting chronic use of intranasal corticoids for symptom control; active disease at both screening and baseline; positive skin test to ≥ 1 perennial allergen of continuous exposure within last two years; wheals induced by skin prick or intradermal injection must have been ≥ 3 mm or ≥ 7 mm, respectively, larger than diluent control; at least moderate (score of 2 on a 4-point scale of 0 to 3, none to severe) rhinorrhea and/or congestion, and a total nasal symptoms score (sum of scores for rhinorrhea, congestion, sneezing, and nasal itching) of at least 5 at screening and for at least 4 of the 7 days just prior to baseline	mometasone QD (200 µg) fluticasone QD (200 µg) placebo x 12 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Mandl 1997 Europe, Latin America and Canada (Fair)	loratadine 10 mg as rescue medication	Severity (4-point scale; 0=none to 3=severe) of individual nasal (sneezing, rhinorrhea, nasal itch, congestion) and non-nasal ocular itch/burning, tearing/watering, redness, and ear/palate itch) symptoms (patient diary assessments) Total nasal symptom score Total symptom score Overall response to therapy (1=excellent to 5=treatment failure)	33.0 years 54.7% Race NR	Duration of perennial rhinitis (years): 12.7 Mean baseline total nasal symptom score: 7 With seasonal allergic rhinitis (% patients): 37.5%	NR/NR/548	76 (14%) withdrawn/15 (2% lost to follow-up/459 (number of patients per treatment group NR)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Mandl 1997 Europe, Latin America and Canada (Fair)	Total nasal symptom score reduction rated by patient/physician (mean percent estimated from figure): 61%/64% vs 55%/55%, NS Mean number of symptom-free days: 10 vs 11, NS Overall condition reduction (physician-rated mean percent reduction): 55% vs 45%, p=0.04 Individual nasal symptom reductions for discharge, congestion, sneezing, itch: no differences for any symptom for any time period	Adverse events were solicited at each treatment visit and the date, time of onset, and duration were recorded; severity of each adverse event was defined as mild, moderate, or severe; investigator assigned each adverse event as unrelated, possibly, probably, or definitely related to study drug	Any adverse event: 60 (33%) vs 70 (38%) Epistaxis/blood in nasal discharge: 30 (17%) vs 32 (17%) Headache: 11 (6%0 vs 17 (9%) Pharyngitis: 10 (6%) vs 17 (9%) Rhinitis: 5 (3%) vs 7 (4%) Nasal burning: 5 (3%) vs 5 (3%) Infection, viral: 5 (3%) vs 1 (1%) Nasal irritation: 4 (2%) vs 5 (3%) Sneezing: 4 (2%) vs 1 (1%) Rhinitis (aggravated): 3 (2%) vs 1 (1%) Somnolence: 3 (2%) vs 2 (1%) Lacrimation: 3 (2%) vs 0 Coughing: 2 (1%) vs 4 (2%) Rhinorrhea; 1 (1%) vs 4 (2%) Dizziness: 0 vs 2 (1%) Rash: 0 vs 2 (1%)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Mandl 1997 Europe, Latin America and Canada (Fair)	Withdrawals due to adverse events: 1% vs 2%, NS Total withdrawals: 16 (9%) vs 22 (12%)	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Sahay 1980 UK (Fair)	RCT, open, parallel, single center	Patients suffering from perennial allergic rhinitis, with or without seasonal allergic rhinitis	flunisolide BID (200 µg) beclomethasone QID (400 µg) x 4 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Sahay 1980 UK (Fair)	Steroid inhalers for asthma were allowed if stable and remained so during study	Sneezing, stuffiness, runny nose, nose blowing, post-nasal drip and epistaxis were all recorded as none (0), mild (1), moderate (2) or severe (3); assessed upon admission and after end of 4 weeks; patients were asked whether symptoms interfered with routine life or sleep; patients assessed the control of their symptoms as total, good, minor, none, or worse	37 years 48% Race NR	Perennial rhinitis with seasonal exacerbation: 76.7% Mean duration of symptoms (years): 12.4 Asthma (% patients): 58.3%	NR/NR/60	6.7% withdrawn/5% lost to follow-up/analyzed unclear

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Sahay 1980 UK (Fair)	Mean change in admission (all NS) Sneezing: –1.44 vs –1.57 Stuffiness; –1.74 vs 1.62 Runny nose: -1.33 vs 1.48 Nose blowing: –1.70 vs –1.72 Post-nasal drip: –0.74 vs –0.68 Epistaxis: –0.15 vs –0.07 Significant change in incidence of interference by symptoms with routine life or sleep: both groups showed change Total control of symptoms (# patients) as rated by doctor/patient: 8/9 vs 9/12	Side-effects were elicited by an indirect question such as 'How is the treatment suiting you?' and if present were classified as possibly or probably related to the test spray	Any side effect: 10 (33.3%) vs 8 (26.7%) Individual side effects probably- or possibly-drug related: Nasal irritation: 3(10%) vs 1 (3.3%) Nasal dryness: 2 (6.7%) vs 3 (10%) Sore throat: 2 (6.7%) vs 1 (3.3%) Hoarseness: 1 (3.3%) vs 1 (3.3%) Nose bleed: 0 vs 3 (10%) Headache: 4 (13.3%) vs 2 (3.3%) Dizziness: 1 (3.3%) vs 1 (3.3%) Nausea: 1 (3.3%) vs 0 Tiredness: 1 (3.3%) vs 0 Confusion: 1 (3.3%) vs 0 Stomatitis: 1 (3.3%) vs 0

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Sahay 1980 UK (Fair)	Withdrawal due to AE: 0 vs 0 Overall withdrawals: 1 (3.3%) vs 3 (10%)	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Adamopoulos 1995 Greece (fair)	Open, randomized, crossover	Patients aged 15-65 years, with symptomatic perennial rhinitis, symptoms duration at least 1 year, suffering from at least 2 symptoms (blocked nose, runny nose, itchy nose, and sneezing) Exclusion: pregnant or lactating women, active or quiescent tuberculosis or an untreated fungal, viral or bacterial respiratory infection, patients with other diseases and conditions which might interfere with the study evaluation or those who required other therapy which would interfere with the study during evaluation	budesonide aqueous 200mcg twice daily vs beclomethasone aqueous 100mcg once daily 6 weeks	None/None
Lebowitz 1993 USA (fair)	Open, randomized	Patients with allergic or vasomotor rhinitis Exclusion: nasal pathology other than rhinitis, patients using antihistamines and/or oral or topical decongestants	triamcinolone 220mcg/d vs. beclomethasone 336mcg/d 8 weeks	None/None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Adamopoulos 1995 Greece (fair)	NR/NR	Primary outcome: daily nasal and eye symptoms (as rated on 4-point scale) secondary outcome: daily eyedrops used, patient assessment, patient period preference	28.9 years 45% Female NR	70% moderate symptoms 25% severe symptoms 5% mild symptoms	NR/NR/40	2/1/37 analyzed
Lebowitz 1993 USA (fair)	None/None	Nasal airflow and total nasal resistance, total symptom score (scale 0-16, comprised of 4 individual symptoms: nasal obstruction, nasal discharge, sneezing, nasal itching) All measurements at initial visit and at 8 weeks	Male: 39 years vs. 43 years Female: 33 years vs. 41 years 60% female	NR	NR/NR/40	10/0/30

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Adamopoulos 1995 Greece (fair)	Total Nasal Symptom Score: 2.13 vs. 2.75, p=0.001 blocked nose: 0.84 vs. 1.07, p=0.004 runny nose: 0.60 vs. 0.87, p=0.0005 itchy nose: 0.28 vs. 0.29, p=0.7 sneezing: 0.41 vs. 0.52, p=0.08 runny eyes: 0.20 vs. 0.23, p=0.3 sore eyes: 0.13 vs. 0.19, p=0.047	Patient self-report	dry nose: 5% vs. 55 epistaxis: 5% vs. 0% gastral discomfort: 0 vs. 3%
Lebowitz 1993 USA (fair)	Mean nasal air flow change: +29% vs. +26% Mean nasal resistance change: -23% vs. -25% Symptom score percent decrease: 54% vs. 58%	NR	NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Adamopoulos 1995 Greece (fair)	3;0	
Lebowitz 1993 USA (fair)	10;0	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Al-Mohaimeid 1993 Saudi Arabia (Fair)	RCT, open, parallel, single center	Age range 18-70 years with symptoms of perennial rhinitis for at least 12 months; presence of at least two nasal symptoms on entry to the study (blocked nose, runny nose, itchy nose, and/or sneezing bouts)	budesonide BID (400 µg) beclomethasone BID (400 µg) x 3 weeks	None
Tai 2003 Taiwan (Fair)	RCT, blinding NR, parallel, single center	Aged 16 to 60; history of moderate-severe perennial rhinitis for at least the previous 6 months; allergen-specific IgE examination verified by MAST CLA, positive response was defined as allergen-specific IgE greater than 0.35 KU/L; during at least half of the run-in period of 1 week, patients must have 2 or more symptoms of nasal blockage, rhinorrhea, sneezing, nasal itching, or postnasal drip of at least moderate severity	fluticasone QD (200 µg) budesonide QD (400 µg) x 8 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Al-Mohaimeid 1993 Saudi Arabia (Fair)	NR	Mean daily score of nasal symptoms (blocked nose, runny nose, itchy nose, sneezing) and ocular symptoms (runny eyes, sore eyes) were score on a 4-point scale (0=no symptoms; 3=severe) (patient diary assessments) Patient global evaluation as ineffective, slightly effective, noticeably effective, very effective or total effective (symptom-free)	30 years 27.5% 90% arabic	Severity of rhinitis: Moderate: 55% Severe: 10.8% Rhinitis duration: < 1 year: 4.2% 1-5 years: 68.3% > 5 years: 26.7%	NR/NR/120	3 (2.5%) withdrawn/0 lost to follow-up/120 analyzed (budesonide n=58; beclomethasone n=62)
Tai 2003 Taiwan (Fair)	loratadine as rescue medication	Primary efficacy parameter: mean nasal symptom score over the treatment period of 8 weeks; total nasal symptom score is the sum of 6 individual symptom scores; daily total score ranged from 0 (best) to 18 (worst) Documentation of nasal symptoms on diary card (nasal blockage, sneezing, nasal itching, rhinorrhea, eye itching) based on a 4-point scale from 0 to 3 Clinic visits at weeks 2, 4, 6 and 8	40.9 years 62.5% Race NR	History of nasal allergy (years): 14.2	NR/NR/24	0 withdrawn/0 lost to follow-up/24 analyzed

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Al-Mohaimeid 1993 Saudi Arabia (Fair)	Mean daily symptom scores at weeks 1/2/3 (*statistically significant) Blocked nose: 1.13/1.02/0.88 vs 1.36/1.10/1.09, NS Runny nose: 0.84*/0.83/0.62 vs 1.12/0.86/0.84 Itchy nose: 0.89/0.67/0.53 vs 1.08/0.88/0.77; NS Sneezing; 0.93/0.61/0.48* vs 1.07/0.81/0.73 Runny eyes: 0.29/0.18/0.12 vs 0.43/0.31/0.30 Sore eyes: 0.32/0.26/0.24 vs 0.35/0.23/0.27, NS Totally symptom-free (% patients): 35% vs 26%, NS % patients that found treatment to be totally effective: 10.4% vs 5.6%, NS	Patients were asked whether they had experienced other symptoms or unusual occurrences since their last visit	Any adverse event: 3 (5.2%) vs 10 (16.1%)
Tai 2003 Taiwan (Fair)	Reduction in total nasal symptom scores (points/% change): 7.77/86% vs 8.01/87.1%, NS Endpoint total nasal symptom scores: 1.23 vs 1.79, NS Mean number of pills of rescue medication: 8.3 vs 11.4, NS	An open-ended area was designed on the nasal symptom diary card for patient to report any adverse event they experience	NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Al-Mohaimeid 1993 Saudi Arabia (Fair)	Withdrawals due to adverse events: 1 (1.7%) vs 0 Overall withdrawals: 3 (5.2%) vs 0	
Tai 2003 Taiwan (Fair)	No withdrawals	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
van As 1993 US (Fair)	RCT, double-blind, parallel, multicenter	Adults and adolescents (at least 12 years of age) with moderate to severe symptoms of perennial allergic rhinitis; positive skin test reaction (≥ 2+) to ≥ perennial allergen; historical evidence of perennial allergic rhinitis; documented nasal eosinophilia; a total symptom score for obstruction plus rhinorrhea of ≥ 100 of 200 possible points on 4 of the preceding 7 days before screening and on 8 of the 14 days during the single-blind placebo run-in period before randomization	fluticasone BID (100 µg) flutacasone QD (200 µg) beclomethasone BID (168 µg) x 6 months	14-day single-blind placebo period

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
van As 1993 US (Fair)	chlorpheniramine maleate 4 mg as rescue medication	Severity of nasal symptoms (obstruction, rhinorrhea, sneezing, and itching) was scored by clinicians at clinic visits after 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 weeks and by patients at the end of each day on 100-point numerical scale (0=no symptoms; 100=severe symptoms); patients also rated nasal obstruction on awakening; overall effectiveness of treatment assessed by clinicians at end of study on 8-point scale (significant to significantly worse)	36.3 years 51.3% Race NR	Duration of rhinitis (% patients): < 1 year: 0.2% 1-5 years: 15.7% 6-10 years: 15.2% 11-20 years: 26.6% > 20 years: 11.8% Unknown: 2.1%	NR/NR/466	106 (22.7%) withdrawn/lost to follow-up NR/number analyzed NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
van As 1993 US (Fair)	Magnitude of improvement at 24 weeks (data NR): ≥ 45% in treatment groups Clinician-rated individual nasal symptom scores for obstruction, rhinorrhea, sneezing, and itching: similar improvements across treatment groups (data NR) Clinician-rated overall assessment: no differences (data NR) Use of rescue medications: no differences (data NR)	NR	Any event: 45 (38%) vs 36 (31%) vs 37 (32%) Sore throat: 2 (2%) vs 2 (2%) vs 2 (2%) Blood in nasal mucus; 11 (9%) vs 5 (4%) vs 11 (9%) Nasal irritation: 0 vs 2 (2%) vs 0 Nasal dryness: 3 (3%) vs 2 (2%) vs 0 Nasal soreness: 3 (3%) vs 0 vs 1 (1%) Nasal burning: 1 (1%) vs 4 (3%) vs 3 (3%) Epistaxis: 17 (14%) vs 18 (15%) vs 10 (9%) Headache: 4 (4%) vs 2 (2%) vs 6 (5%)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
van As 1993 US (Fair)	Total withdrawals: 27 (23%) vs 16 (14%) vs 31 (27%), p-value NR Withdrawals due to adverse events: 6 (5%) vs 4 (3%) vs 10 (9%), NS	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Bende 2002 Sweden, Spain, Hungary, and Portugal (Fair)	RCT, blinding NR, parallel, multicenter	Adults > 18 years of age and had ≥ 2-year history of perennial allergic rhinitis attributable to house-dust mite, dog, or cat allergens, or molds; allergy verified by a positive skin prick test of radioallergosorbent test within 2 years before the study, or by a positive skin prick test on enrollment; patients who were allergic only to dog or cat had to be exposed to the allergens during the study period to be eligible for inclusion; morning or evening NIS of ≥ 3 on 4 days (not necessarily consecutive), and a symptom score for blocked nose of ≥ 1 on 4 days during the last day of the run-in period	budesonide QD (256 µg) budesonide QD (128 µg) mometasone QD (200 µg) placebo x 4 weeks	2-week run-in period during which they recorded symptom scores for blocked nose, runny nose, and the worst of itchy nose or sneezing each morning and evening on a 4-point scale (0=no symptoms; 3=severe)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bende 2002 Sweden, Spain, Hungary, and Portugal (Fair)	loratadine 10 mg as rescue medication	Primary efficacy: Nasal Index Score (sum of individual symptom scores: blocked nose, runny nose, itchy nose or sneezing) Secondary: Individual symptom scores; onset of action; number of rescue medication tablets taken; patients' overall evaluation of treatment efficacy Patients evaluated the ability of the study medication to control their nasal symptoms at weeks 2 and 4 on a 5-point scale (0=no control to 4=total control)	31.0 years 57.7% Race NR	Weight (kg)=69.6 Height (cm)=169.7 Years with rhinitis=10.1 Smokers=17.2%	NR/563/438	37 (8.4%) withdrawn/lost to follow-up NR/413 analyzed (budesonide 256 n=99; budesonide 128 n=107; mometasone n=103; placebo n=104)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Bende 2002 Sweden, Spain, Hungary, and Portugal (Fair)	NIS (adjusted mean change in morning/evening): -1.45/-1.59 vs -1.41/-1.50 vs -1.26/-1.44, NS % patients experiencing no symptom control: 5.9% vs 10.1% vs 7.6%, NS Weekly consumption of rescue medication: 1.18 vs 1.31 vs 1.23, NS Onset of action stat. significant improvements in NIS compared with placebo after 4h: p=0.046 vs. p=0.010 vs. p=0.014	Information about adverse events was requested at the end of the run-in period and after 2 and 4 weeks of treatment; the dates of onset and recovery, maximum intensity, action taken, and, if applicable, final outcome of each event were recorded	Headache: 11% vs 11% vs 9% Respiratory infection: 5% vs 3% vs 7% Epistaxis: 9% vs 6% vs 6% Viral infection: 7% vs 1% vs 3% Pharyngitis: 1% vs 1% vs 3%

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Bende 2002 Sweden, Spain, Hungary, and Portugal (Fair)	Total withdrawals: 13 (12.1%) vs 6 (5.4%) vs 5 (4.7%) Withdrawals: 5 (4.7%) vs 1 (0.9%) vs 2 (1.9%)	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Bunnag 1984 Thailand (Fair)	Non-randomized controlled trial, open, crossover, single center	Perennial allergic rhinitis	flunisolide BID (200 µg) beclomethasone QID (400 µg) x 4 weeks	None
Haye 1993 UK (Fair)	RCT, double-blind, parallel, multicenter	Aged ≥ 16; ≥ 2-year history of perennial rhinitis (≥ 1 symptom at time of entry: nasal blockage, nasal discharge, nasal itching, sneezing); experienced symptoms throughout the year; symptoms severe enough to warrant treatment	fluticasone BID (200 µg) beclomethasone BID (200 µg) for up to one year	2-week single-blind placebo run-in; no washout

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Bunnag 1984 Thailand (Fair)	chlorpheniramine maleate 4 mg or a combination of tripolidine HCl 2.5 mg and pseudoephedrine HCl 60 mg as rescue medication	Itching, sneezing, stuffiness and running nose, each rated on a 4-point scale (0=none, 1=slight, 2=moderate, 3=severe); assessed on admission and at end of each test medication period by blinded physicians	28.5 years 66.7% Race NR	Duration of symptoms: 7.3 years Concomitant bronchial asthma (% patients): 4 (8.3%)	NR/NR/48	3 (6.2%) withdrawn/0 lost to follow-up/45 evaluated
Haye 1993 UK (Fair)	terfenadine 60 mg tablets as rescue medication	Patients asked to classify their symptoms of sneezing, nasal itching, nasal discharge, nasal blockage and eye watering/irritation according to a score of 0-3 (0=none; 3=severe) Treatment response assessed after 4 weeks, then at 12 weekly intervals	37.6 years 56.6% female Race NR	Weight (kg)=67.6 Height (cm)=168.8	NR/NR/251	72 (28.7%) withdrawn/lost to follow-up NR/242 analyzed (fluticasone n=159 vs beclomethasone n=83)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Bunnag 1984 Thailand (Fair)	Mean change in total symptom score (all p<0.0005): Periods I and II combined: -2.91 vs -4.96 Period I only (before crossover): -3.33 vs -5.40 Period II only: -2.76 vs -3.75 Drugs rated 'very effective' by: Patients: 9 (20%) vs 11 (24.4%), NS Physicians: 4 (8.9%) vs 6 (13.3%), NS	NR	Any side effects considered to be probably drug-related: 9 (20%) vs 3 (6.6%) Burning sensation: 9 (20%) vs 1 (2.2%), p= 0.0081 (2-sided Fisher's exact test calculated using StatsDirect) Nasal irritation: 2.2% vs 0, NS Nasal obstruction: 0 vs 2.2%, NS Throat dryness: 0 vs 2.2%, NS Headache: 2.2% vs 2.2%, NS Dizziness: 0 vs 2.2%, NS Insomnia+nightmare: 0 vs 2.2%, NS Rash: 2.2% vs 0, NS
Haye 1993 UK (Fair)	Overall symptom grades (% patients with severity of none/mild/moderate-severe: data NR only p-value/% patients with severity of none estimated from graph) Nasal discharge: p=0.002/none=67% vs 48% Nasal blockage: p=0.002/none=48% vs 51%, Eye watering/irritation: p=0.048/none=75% vs 69% Sneezing: p=0.114/none=63% vs 55% Nasal itching: p=0.052/none=75% vs 62%	Adverse events were both spontaneously by the patient at any stage during the study and those invoked by the investigator at each clinic visit Serious adverse events defined as: (1) all deaths; (2) life-threatening events; (3) events which were disabling or incapacitating; (4) events which required prolonged hospitalization; (5) clinical or laboratory events which led to withdrawal of the drug; (6) any congenital abnormality or cancer or drug overdose	Serious adverse events (% patients): 4% vs 4% Overall adverse events (% patients): 55% vs 58% Upper respiratory tract infections: 17% vs 17%, NS Epistaxis: 14% vs 5%, p=0.0285 (2-sided Fisher's exact test performed using StatsDirect) Headache: 8% vs 4%, NS

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Bunnag 1984 Thailand (Fair)	Withdrawals due to adverse events: 1 (2.2%) vs 0, NS Overall withdrawals: NR by treatment group	
Haye 1993 UK (Fair)	Overall withdrawals: 43 (27%) vs 20 (24%), NS Withdrawals due to adverse events NR	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Day 1998 Canada/Spain (Fair)	RCT, double-blind for budesonide and placebo and investigator-blinded for fluticasone, parallel, multicenter	Patients aged 18 years and older with a least a 1-year history of allergic perennial rhinitis were considered for entry into the study; diagnosis verified by a positive skin prick test response to 1 or more perennial allergens performed within 1 year of the start of the study; exhibit ≥ 2 of 3 symptoms of rhinitis (blocked nose, runny nose, or sneezing) with severity rated ≥ 1 on a 0-3 symptom severity scale during ≥ 8 of the 8- to 14-day baseline period	budesonide QD (256 µg) fluticasone QD (200 µg) x 6 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Day 1998 Canada/Spain (Fair)	loratadine 10 mg as rescue medication	Primary efficacy variables: mean scores of 3 individual and combined nasal symptoms (blocked nose, runny nose, and sneezing) as rated by the patients using the 4-point scale (0=no symptoms, 3=severe) Other variables: Onset of action assess by comparison of change from baseline in combined nasal symptoms score for each active treatment with that of placebo for the first 4 consecutive scoring intervals (i.e., within 12, 36, 60 and 84 hours) Patient's overall evaluation of efficacy: patients rated the medication's overall ability to control their nasal symptoms using a 5-point scale (0=symptoms were aggravated; 4=total control)	30.8 years 54.9% female Race NR	Mean disease duration (yrs): 11.4	NR/NR/314	Withdrawn=NR/lost to follow-up NR/analyzed: efficacy=273 (n=111, n=109, n=53) Safety=303 (sample sizes for different groups NR)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Day 1998 Canada/Spain (Fair)	Reduction in combined nasal symptom scores: -2.11 vs -1.65, p=0.31 Reductions in individual symptoms: Nasal blockage: -0.75 vs -0.5, p=0.009 Runny nose: -0.73 vs -0.59, NS Sneezing: -0.66 vs -0.55, NS Eye symptoms: NS for either treatment vs placebo Onset of action (# hours before significant step-score reduction): 36 vs 60, pairwise comparison NR Patients' overall evaluation of treatment efficacy (% patients who reported substantial/total control): 3 weeks: 70.1% vs 61.0%, NS 6 weeks: 67.5% vs 65.3%, NS Reduction in rescue medication use: -0.74 vs -0.74, NS	At randomization and after 3 and 6 weeks of treatment, patients were asked whether they had experienced any adverse events; investigator rated severity (mild, moderate, severe)	Overall adverse events (% pts): 46% vs 37% Bloody nasal discharge: 22 (18%) vs 8 (7%), NS Respiratory infection: 12 (10%) vs 8 (7%), NS Headache: 11 (9%) vs 12 (10%), NS Pharyngitis: 5 (4%) vs 3 (2%), NS

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Day 1998 Canada/Spain (Fair)	Overall withdrawals: 4 (3.6%) vs 3 (2.7%), NS Withdrawals due to adverse events: 2 (1.8%) vs 2 (1.8%), NS	Supported by Astra Draco, (makers of BUD)

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Meltzer 1990 US (Fair)	RCT, double-blind, parallel, multicenter	Aged 14 to 65 years with a history of symptoms of perennial allergic rhinitis for ≥ 2 years that required medication most of the time; a positive skin test to a perennial allergen, such as house dust mite or mold, within the previous 2 years was required; during the baseline period for 1 week before the study, patients' nasal symptoms had to be severe enough to require the chlorpheniramine for ≥ 4 of 8 days	flunisolide ***original*** formulation BID (200 µg) flunisolide ***new*** formulation BID (200 µg) x 4 weeks In the new formulation, propylene glycol was decreased from 20% to 5%, polyethylene glycol was increased from 15% to 20% and 2.5% polysorbate was introduced	None
Poor quality studies				
Naclerio 2003 US (Poor)	RCT Blinding: Investigator blinded but unclear if patients blinded Setting: Unclear	Subjects over age 18 years, with rhinitis symptoms on the majority of days of each year and a positive skin test to dust mites	budesonide 128 ug/day (1) mometasone 200 ug/day (2) x 2 weeks	None

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Meltzer 1990 US (Fair)	chlorpheniramine 4 mg as rescue medication	Patients scored symptoms (runny nose/sniffing, stuffy nose, sneezing/itchy nose, postnasal drip/snorting) on a scale of 0=absent to 4=very severe; patients were evaluated in the office at 2 and 4 weeks Global evaluation by patient and investigator summarizing the efficacy and acceptability of the sprays, rated using a VAS scale of 1=totally ineffective or unacceptable to 100=totally effective or acceptable	33.7 years 64.2% female Race NR	NR	NR/NR/220	NR/NR/analyzed: efficacy=210 (original n=98; new n=103); safety=215
Poor quality studies						
Naclerio 2003 US (Poor)	NR	Rhinitis Quality of Life Questionnaire at baseline and after 2 weeks	budesonide vs mometasone (sample sizes NR; overall mean calculations not possible) Age: 25.9 vs 25.4 % male: 40 vs 60 % white: 90 vs 60	Skin test (wheal mm): 9.6 vs 9.7 RQLQ Overall score (estimated from figure): 1.7 vs 2.4	NR/NR/22	3/0/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Meltzer 1990 US (Fair)	Total symptom score reduction (estimated from figure): -2.8 vs -2.4, NS Median time to measurable symptom relief (days): 4 vs 4, NS Mean reductions in individual symptom scores (estimated from figure): Sniffing: -0.9 vs -0.6, NS Sneezing: -0.8 vs -0.7, NS Stuffiness: -0.7 vs -0.8, NS Postnasal drainage: -0.5 vs -0.7, NS Decrease in mean number of chlorpheniramine 4-mg tablets/day: -0.6 vs -0.5, NS Acceptability of nasal burning/stinging: 52 vs 87, p<0.001 Overall effectiveness (% improvement on VAS scale): 70% vs 75%, NS	Patients reported adverse events	Additional adverse experiences included: blood in mucus, sore throat, nasal dryness, and post-nasal drainage (rates NR)
Poor quality studies			

Naclerio 2003
US
(Poor)
	RQLQ mean change (estimated from figure): -0.7 vs -1.4, NS	NR	Total # patients (stratification by group NR):
			Headache=6
			Increased postnasal drip=2
			Blood-tinged nasal secretions=1
			Menstrual cramps=1
			Pharyngitis=1
			Muscle soreness=2

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Meltzer 1990 US (Fair)	Withdrawals due to adverse events: 2 patients in each group (denominators NR) Overall withdrawals NR	
Poor quality studies		
Naclerio 2003 US (Poor)	Total: 2 AE withdrawals: 0	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Grubbe 1996 US (Poor)	RCT, single-blind, multicenter, parallel-groups	Male and female patients 12 to 70 years of age with a diagnosis of perennial allergic rhinitis for at least the preceding 2 years; diagnosis verified by positive skin test to perennial allergens such as molds and dust mites; total nasal symptom score ≥ 24 on 4 of 5 of the baseline period	budesonide 128 ug/day (1) mometasone 200 ug/day (2) x 2 weeks	No run-in/5-day washout
McAllen 1980 UK (Poor)	Randomized, double-blind, crossover	Aged 16 to 60; suffering from moderate to severe perennial rhinitis with or withour seasonal exacerbations	triamcinolone 220 ug/d QD (2) beclomethasone dipropionate aqueous spray 336 ug/d BID (2) x 4 weeks	NR/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Grubbe 1996 US (Poor)	None	Primary outcome: Change from baseline in Total Nasal Symptom Score Secondary: Change scores for each nasal symptom; Global evaluation of treatment effectiveness rated by physicians using a 5-point scale (0=no relief, 1=slight relief, 2=moderate relief, 3=marked relief, 4=complete relief) at 2 and 4 weeks; onset of action in first 7 days	32.3 yrs 47.9% male 86.9% white 8.0% black 2.2% hispanic 1.9 oriental 0.9% asian, mideastern, or arabic	Years of allergic rhinitis: 17.8 Total Nasal Score: 8.9	NR/NR/313	32 (10.2%)/3 (0.9%)/unclear for efficacy; 313 for AE's (triamcinolone n=154, beclomethasone n=159)
McAllen 1980 UK (Poor)	NR/NR	Patient report	19.0yrs / 58.0yrs 16 male 18 female	100% patients with mod-severe symptoms Seasonal exacerbations: 7 positive reaction to skin tests for allergens: 22	NR/NR/34	3/1/30 analyzed

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Grubbe 1996 US (Poor)	Improvement in total nasal symptom score (% change): 47% vs 46%, NS Physician's ratings of moderate-complete relief of rhinitis symptoms (% patients): 77% vs 74%, NS	Patient rating of daily questionnaire using 5-point scale (0=not bothersome, 4=extremely bothersome): 1. Some of the medicine ran down my throat 2. Some of the medicine ran out of my nose 3. The medicine tasted bad, left a bad taste 4. It made me sneeze 5. It made my throat sore 6. It made my nose sting and/or burn 7. It made my nose bleed 8. It dried the inside of my nostrils 9. There was blood in my nasal mucus when I blew my nose 10. It made my nose feel stuffed up	% patients Overall AE (% pts): 36% vs 47%, p-value NR Medication running down throat: 54% vs 16%; p=0.001 Medication running out of the nose: 33% vs 6%; p=0.001 Increased rhinitis: 6% vs 12% Headache: 6% vs 7%
McAllen 1980 UK (Poor)	Patient report of control of symptoms at 4 weeks:` Worse: F: NR vs B: NR None: F: 5 vs B:2 Minor: F: 7 vs B: 8 Good: F: 7 vs B: 20 Complete: F: 4 vs B: 3	Patient self-report	Reasons to discontinuation: flunisolide: 1 mild, persistent nose bleeds beclomethsane dipropionate: 1 feeling tiredness and apathy

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Grubbe 1996 US (Poor)	Withdrawal due to AE: 3% vs 6%; p-value NR Overall withdrawals: 5.8% vs 14.5%, p-value NR	
McAllen 1980 UK (Poor)	4;2	

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Study design, Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Svendsen 1989 Denmark (Poor)	Randomized, double-blind, crossover	Patients with active rhinitis defined as having two or more symptoms. Exclusion: immunotherapy within 6 months before study, structural abnomalities in the nose, pregnancy, receiving treatment for other diseases not included in study	nebulized aqueous flunisolide, 25g, twice daily vs aqueous beclomethasone dipropionate, 25g, twice daily Study duration: 8 weeks	2 weeks/NR
Scadding 1995 UK (Poor)	Randomized, double-blind, parallel Multicenter	Patients with over 12 years of mod-severe history of perennial arthritis, positive skin test for allergens	fluticasone propionate aqueous nasal spray 100g once daily vs 100g twice daily beclomethasone dipropionate aqueous nasal sppray, 200g, twice daily vs placebo Study duration: 12 weeks	2 weeks/NR
Klossek 2001 France (Poor)	Randomized, open-label, parallel Multicenter	Patients aged 18-65, with perennial allergic rhinitis vascconstrictors one month before study, corticosteroids or astemizole 3 months before study, of at least one year. Exclusion: positive skin test, positive assay for specific IgE	triamcinolone acetonide aqueous intranasal spray, 200g/daily Study duration: 6 months	NR/NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Svendsen 1989 Denmark (Poor)	Beta-agonists, theophyllamines or inhaled steroids allowed for asthma patients	Peak expiratory flow measured by low-range peak-flow meter, posterior rhinomanometry performed between treatments	NR	Patients with bronchial asthma: 15	NR/NR/23	NR/NR/NR
Scadding 1995 UK (Poor)	terfenadine, 60mg tablets as rescue medication	Patient daily diary, weekly clinic visits	Mean age: 34.8 years 46.5% Male Ethnicity: Caucasian: 96.2% vs Asian: 1%; Oriental: 1%; Black: 1%	Skin prick test: positive: FPod: 46% FB bd: 47% BDP: 53% placebo: 51% Skin prick test: negative: FPod: 54% FB bd: 53% BDP: 47% placebo: 49%	622/516/371	NR/NR/NR
Klossek 2001 France (Poor)	NR/NR	Nasal mucosal thickness, macroscopic appearance, mucocillary function assessed as clinical visits	Mean age: 27 years Male: 60% Ethnicity NR	Mean duration of PAR: TAA: 11.7 BDP: 8.5 cetririzine: 11.2	NR/92/82	0/0/82

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Results	Method of adverse effects assessment	Adverse Effects Reported
Svendsen 1989 Denmark (Poor)	Difference at of symptoms at 8 weeks from baseline: Posterior rhinomanometry (degrees): B: -41 vs F: -7 Nasal peak flow (morning): B: -12 vs F: -13 Nasal peak flow (evening): B: -33 vs F: -5	Patient self-report	Increasing pattern in nasal peak flow during the first treatment period, for both drugs: p<0.05
Scadding 1995 UK (Poor)	Symptom relief at 12 weeks: Sneezing: FPod: 19% vs vs FPbd: 25% vs placebo: 7% Rhinohoea: FPod: 19% vs FPbd: 15% vs placebo: 3% Overall symptoms: FPod: 13% vs FPbd: 14% vs placebo: 4% Nasal blockage: FPbd: 16% vs placebo: 7%; p=0.015	Patient self-report	Increasing pattern in nasal peak flow during the first treatment period, for both drugs: p<0.05
Klossek 2001 France (Poor)	Mean change of nasal mucosa thickness: TAA: 9.5 microns BDP: 6.0 microns cetirizine: 7.7 microns	NR	NR

Evidence Table 5. Head-to-head trials in patients with PAR

Author Year Country Trial Name (Quality Score)	Total withdrawals; withdrawals due to adverse events	Comments
Svendsen 1989 Denmark (Poor)	NR;NR	
Scadding 1995 UK (Poor)	NR;NR	
Klossek 2001 France (Poor)	NR;NR	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Chervinsky 2007 US	Randomized, double-blind placebo-controlled trial Multicenter	Age ≥12 years with a history of PAR with demonstrated sensitivity through skin prick test to at least 1 allergen know to induce PAR	ciclesonide 200µg/day placebo	7-14 day run-in (rescue medications allowed)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Chervinsky 2007 US	NR (also see column E)	No primary efficacy oucomes (safety study) Patient-rated reflective TNSS and individual NSS, physician evaluation of overall nasal signs/symptoms at 52 wks; RQLQ at 24 and 48 wks	Mean age 37 yrs 34% male 81% White 10% Black 9% Other	Mean baseline TNSS: 6.37 Mean baseline RQLQ: 2.85	903/NR/663	189/NR/663

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Chervinsky 2007 US	Mean change from baseline in TNSS at 52 wks: ciclesonide -2.3 vs placebo -1.8 (mean difference 0.6; CI 0.3-0.9) p<0.001 PANS: no differences between groups (data not shown) Mean change in RQLQ: ciclesonide -1.07 vs placebo -0.88 (mean difference 0.19; CI 0.01-0.36) p=0.04	Patient self report; physical exams, vital sign monitoring and laboratory testing at baseline, 24, 48 and 52 wks. Ocular exam, 24-hour urine and plasma cortisol, ECG baseline and weeks 24 and 48	Withdrawals due to AEs: ciclesonide 19/441 (4%) vs placebo 6/222 (3%) Patient reporting any adverse event: ciclesonide 331/441 (75%) vs placebo 165/222 (74%) Severe AE rates: ciclesonide 16/441 (4%) vs placebo 6/222 (3%) Other AEs:ciclesonide vs placebo URTI 72/441 (16%) vs 39/222 (18%) Nasopharyngitis 58/441 (13%) vs 40/222 (18%) Epistaxis 44/441 (10%) vs 16/222 (7%) Pharyngolaryngeal pain 41/441 (9%) vs 10/222 (4.5%) Sinusitis 41/441 (9.3%) vs 16/222 (7/2%) Headache 33/441 (8%) vs 13/222 (6%) Nasal discomfort 20/441 (5%) vs 9/222 (4%) Cough 19/441 (4%) vs 5/222 (2%) Bronchitis 18/441 (4%) vs 8/222 (4%) Influenza 17/441 (4%) vs 8/222 (4%)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Chervinsky 2007 US	189/25	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Meltzer 2006 US	Randomized, double-blind placebo-controlled trial Multicenter	Age >12 yrs in good health with at least 2-year history of PAR requiring continuous or intermittent treatment in the past, demonstrated skin prick test sensitivity to at least 1 allergen know to induce PAR	ciclesonide 200µg/day placebo	7-14 day run-in

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Meltzer 2006 US	Immunotherapy if maintenance regimen unchanged for 30 days prior to study entry	Change from baseline in reflective TNSS (average of morning and evening scores) recorded days 1-42; also PANS and RQLQ	Mean age 36 yrs 35% male Ethnicity NR	Baseline TNSS (average of morning and evening scores) 7.65	676/NR/471	62/NR/NR for efficacy (reported as all randomized pts who received at least one dose of study medication and had at least one post-baseline measurement)/471 for safety

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Meltzer 2006 US	Mean change from baseline in TNSS at 6 wks: ciclesonide -2.51 vs place -1.89; mean difference 0.63; p<0.001 Mean change in physician evaluated nasal signs and symptoms at 6 wks: ciclesonide -2.05 vs placebo -1.67; p=0.051 Mean change in RQLQ at 6 wks: ciclesonide -1.30 vs placebo -1.01; p=0.01	General physical exams, vital signs, laboratory evaluations	Ciclesonide vs placebo Any AE: 102/238 (43%) vs 110/233 (47%) Withdrawals due to AEs: 10/238 (4%) vs 11/233 (5%) Specific AEs: Headache 21/238 (9%) vs 17/233 (7%) Epistaxis 18/238 (8%) vs 12/233 (5%) Nasopharyngitis 15/238 (6%) vs 16/233 (7%) Pharyngitis 9/238 (4%) vs 9/233 (4%) URTI 8/238 (3%) vs 16/233 (7%) Cough 5/238 (2%) vs 5/233 (2%) Sinus headache 5/238 (2%) vs 2/233 (1%) Nasal passage irritation 3/238 (1%) vs 5/233 (2%) Asthma exacerbation 1/238 (<1%) vs 5/233 (2%) Nausea 1/238 (<1%) vs 5/233 (2%)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Meltzer 2006 US	62/21	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Rosenblut 2007 13 countries	Randomized, double-blind placebo-controlled trial Multicenter	Age ≥12 years with a history of PAR with demonstrated sensitivity through skin prick test to at least 1 allergen know to induce PAR	fluticasone furoate 110µg/day placebo	7-14 day TNSS screening

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Rosenblut 2007 13 countries	up to 10mg/day loratadine as rescue therapy	study not designed to assess efficacy	Mean age 32 yrs 49% male 87% White <1% Black 11% American Hispanic 2% Other	NR	984/NR/810	214/13/806 (4 post-randomization exclusions)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Rosenblut 2007 13 countries	NR	Patient self report with physician evaluation every 4 wks, laboratory testing, ECG, physical exam at 12, 24 and 52 weeks	Fluticasone furoate vs placebo Any AE 464/605 (77%) vs 142/201 (71%) Withdrawals due to AEs 38/605 (6%) vs 7/201 (3%) Headache 186/605 (31%) vs 69/201 (34%) Nasophayrngitis 157/605 (26%) vs 51/201 (25%) Phayrngolaryngeal pain 53/605 (9%) vs 18/201 (9%) Back pain 39/605 (6%) vs 12/201 (6%) URTI 37/605 (6%) vs 16/201 (8%) Influenza 32/605 (5%) vs13/201 (6%) Cough 29/605 (5%) vs 7/201 (3%) Upper abdominal pain 23/605 (4%) vs 11/201 (5%) Toothache 29/605 (5%) vs 5/201 (2%) Dysmenorrhea 22/605 (4%) vs 8/201 (4%) Pyrexia 21/605 (3%) vs 9/201 (4%) Ear pain 10/605 (2%) vs 8/201 (4%) Epistaxis 20/605 (20%) vs 8/201 (17%) Rhinitis 14/605 (2%) vs 3/201 (1%) Rhinorrhea 10/605 (2%) vs 6/201 (3%) Nasal discomfort 5/605 (<1%) vs 3/201 (1%)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Rosenblut 2007 13 countries	214/45	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Dahl 2005 Denmark good	Randomized controlled double-blind parallel multicenter	aged 12 years and above, with an established clinical history of pollen-induced asthma and rhinitis during two of the last three seasons and positive skin test or radioallergosorbant test to relevant pollen allergens. All had normal lung function and no signs oor symptoms of asthma outside the pollen season.	fluticasone aqueous nasal spray (INFP) 200mcg once daily and inhaled fluticasone (IHFP) 250mcg BID or INFP and inhaled placebo or intranasal placebo and IHFP or intranasal and inhaled placebos Study period: 6 weeks	NR
Gurevich 2005 USA fair	randomized, double-blind, contoleed, crossover	18-65 year old men and women with year-round nasal congestion, poor sleep, daytime fatigue, positive skin test response for a perennial allergen, negative sking test result for seasonal allergens, free of other diseases and able to be on placebo without significant compromise in quality of life.	budesonide 128mcg once daily vs. placebo Study period: 8 weeks total, 3 weeks each treatment arm with run-in and washout	1-week run-in with nasal saline solution once daily, two sprays in each nostril 1-week washout between study arms same as run-in

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Dahl 2005 Denmark good	rescue medication: inhaled salbutamol, intraocular levocabastine and oral acrivastine	diary card measures: morning and evening peak expiratory flow daily during the entire study. Patient record of daytime and nighttime asthma and rhinitis symptoms use of rescue medication	INFP+IHFP vs. IHFP vs. INFP vs. placebo mean age, years (SD): 34.9(12.6) vs. 33.1(9.5) vs. 35.5(11.1) vs. 31.8(10.7) female, %: 57 vs. 41 vs. 44 vs 52 ethnicity NR	NR	275/NR/262	26/1/236
Gurevich 2005 USA fair	None	daily diaries: subjective sleep measures Epworth sleepiness scale (ESS) Rhinitis Severity Score (RSS) Functional OUtcome Sleep Questionnaire (FOSQ) Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)	mean age: 46.3 years female: 65.4% ethnicity: NR	NR	NR/NR/26	0/0/26

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Dahl 2005 Denmark good	INFP+IHFP vs. IHFP vs. INFP vs. placebo (estimated from graphic) % difference with no nasal blockage: 8 vs. 25 vs. 12 vs. 40% % difference with no sneezing: 15 vs. 26 vs. 3 vs. 37% % difference with no rhinorrhea: 15 vs. 32 vs. 6 vs. 33% significant differences in all nasal found only for those patients taking nasal corticosteroids compared to placebo	patient self-report	INFP+IHFP vs. IHFP vs. INFP vs. placebo 28% vs. 30% vs. 27% vs. 29%
Gurevich 2005 USA fair	budesonide vs. placebo all outcomes measured by symptom improvement, mean change RSS: -0.62 vs. 0.01 for nasal congestion, p=0.04, -0.71 vs. 0.04, p=0.01 all other rhinitis symptoms NSD subjective sleep measures: total sleep score: 0.54 vs. -0.74, p=0.04 sleep compared with absolute: 0.35 vs. -0.3, p=0.01 refreshing and restorative sleep: 0.19 vs. -0.39, p=0.04 total ESS: -1.5 vs. 0.9, NSD total FOSQ: 0.75 vs. 0.04, NSD RQLQ: NSD in any of the sleep domaines	NR	NR

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Dahl 2005 Denmark good	26/9	
Gurevich 2005 USA fair	0/0	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Murphy 2006 USA fair	randomized, double-blind, placebo-controlled multi-center	Prepubertal children with perennial AR were screened at 28 centers on the United States. Inclusion criteria for the baseline period (visit 1) included prepubertal boys aged 4 to 8 years and prepubertal girls aged 4 to 7 years; Tanner stage 1 classification for sexual maturity; a 1-year or longer history of perennial AR and a canidate for treatment with nasal corticosteroids; positive response to a skin prick test for perennial allergens; height and weight within 5th through 95th percentiles; and ability to demostrate effective use of the study medication device at the end of the 6-month base-line period.	Budesonide aquesous 64mcg once daily or placebo Study period: 12 months	6 month baseline period where medications that could affect growth were not allowed. To establish a baseline growth velocity for each patient.

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Murphy 2006 USA fair	rescue medication: combination of carbinoxamine and pseudoephedrine. Other rescue meds that did not affect growth were allowed	Height measured with stadiometer at 3,6, 9 and 12 months	Budesonide group: Male 5.9y, female 5.9y, 63% Male, 37% female, 75% white, 11% black, 8% hispanic, 6% other. Placebo group: Male 5.9y, female 5.9y, 73% Male, 27% female, 76% white, 11% black, 5% hispanic, 7% other.	Budesonide vs. placebo group mean Growth velocity,cm/yr (SD) 6.7(2.4) vs. 6.6 (2.0) mean height, cm (SD) 121.8(8.9) vs. 121.2 (8.5)	407/NR/229	61/13/191

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Murphy 2006 USA fair	budesonide vs. placebo mean difference in growth velocity from baseline to 1 year: 5.91 +/-0.11vs. 6.19 +/-0.16 cm per year 0.27 +/-0.18 cm per year (95%CI, -0.07 to 0.62 cm per year), no significant treatment effect. %age of patients with quartile for GV increased or remained unchanged during 1 year treatment: 60 vs. 67%, p=0.42 %age of patients with GV below 3rd percentile during 1 year treatment: 8.5 vs. 3.3%, p=0.23 %age of patients with percentile for height decrereased from that at baseline during 1 year treatment: 59 vs. 54%, p=0.64 mean change in height from baseline: 5.83 vs. 6.17 cm	patient self-report	Budesonide (N=155) vs. Placebo (N=74) No. (%) Pyrexia 27(17) vs. 13(18) Cough 26(17) vs. 11(15) Nasopharyngitis 25(16) vs. 12(16) Headache 25(16) vs. 11(15) Upper respiratory tract infection 22(14) vs. 19(26) Streptococcal pharyngitis 19(12) vs. 11(15) Otisis media 17(11) vs. 7(9) Sinusitis 10(10) vs. 8(11) Viral Infection 9(6) vs. 9(12)

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Murphy 2006 USA fair	61/8	

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Study design Setting	Eligibility criteria	Interventions (total daily dose)	Run-in/washout period
Stelmach 2005 Brazil fair	Randomized controlled double-blind parallel multicenter	positive skin-prick test results for one or more allergens, nonsmokers or ex-smokers with <7 packs/year up to one year before the beginning of the study, no immunotherapy or hospitalization due to an asthma exacebation during the previous 6 months, no use of oral, injected or inhaled corticosteroids and no respiratory infection during the 4 weeks preceding the study, no current use of theoplhylline or leukotriene antagonists adn the abscence of a history of antiinflammatory drug-induced asthma.	nasal group: beclomethasone nasal spray, 400mcg/day vs. placebo metered-dose inhaler (MDI) pulmonary group: beclomethasone MDI, 1000 mcg/day vs. nasal spray placebo nasal-plus-pulmonary group: beclomethasone nasal spray, 400mcg/day vs. beclomethasone MDI, 1000 mcg/day	2 week run-in with placebo nasal spray and MDI

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender (% female) Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Stelmach 2005 Brazil fair	rescue medications: Salbutamol and short courses of type 1 antihistamines	Self-assessed diary symptom scores, change from 2 to 16 weeks: Rhinitis symptom score Asthma symptom score Total symptom score Rhinitis clinical questionnaire,change from 2 to 16 weeks Asthma clinical questionnaire, change from 2 to 16 weeks	mean age: 25.4y female: 57.6% Ethnicity: NR	nasal vs. pulmonary vs. nasal + pulmonary group Duration of Asthma, yr.: 15 vs. 12 vs.17, nsd duration of rhinitis, yr.: 13 vs. 10 vs.11, nsd Rhinitis diary score: 4.35 vs. 3.07 (p=0.02) vs. 4.03 Asthma diary score: 2.64 vs. 2.85 vs. 3.04, nsd Rhinitis clinical questionnaire: 6.9 vs.7.7 vs. 7.5, nsd Asthma clinical questionnaire: 15.0 vs. 18.9 vs. 18.5, nsd	NR/74/59	15/NR/59

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Results	Method of adverse effects assessment	Adverse effects reported
Stelmach 2005 Brazil fair	nasal vs. pulmonary vs. nasal + pulmonary group Self-assessed diary symptom scores, change from 2 to 16 weeks: Rhinitis symptom score: -.1.29 vs. -0.13 vs. -1.63, p=0.002 Asthma symptom score: -0.97 vs. -0.70 vs. -0.66, p=0.0001 Total symptom score: -2.26 vs. -0.81 vs. -2.3, p=0.0002 Rhinitis clinical questionnaire,change from 2 to 16 weeks : -1.9 vs. 0.1 vs. -0.9, nsd Asthma clinical questionnaire, change from 2 to 16 weeks: -4.2 vs. -3.6 vs. -7.6, p=0.009	NR	NR

Evidence Table 5a. Placebo-controlled trials in patients with PAR

Author Year Country	Total withdrawals/ withdrawals due to adverse events	Comments
Stelmach 2005 Brazil fair	15/NR	

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Naclerio 2003 US	NR	NR	No, budesonide group had better RQLQ Emotional domain score (p=0.04) and a trend toward more white patients (p=0.052)	Yes	Unclear	Unclear
Shah 2003	Yes	Single-blind, yes	Yes, some differences in gender and ethnicity	Yes	Yes	No

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	*External Validity* Number screened/ eligible/ enrolled
Naclerio 2003 US	Y/N/N/N	None	Unclear	No	Poor	NR/NR/22
Shah 2003	Yes, Yes, Yes, No	No	Yes	No	Fair	NR/NR/n=181 in Study I and n=190 in Study II

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Naclerio 2003 US	Confounding medical problems or required daily medication except for birth control pills or inhalers to control asthma	None	No	Yes	Astra Zeneca	Yes
Shah 2003	Pregnancy, nursing, or not using accepted method of birth control presence of nasal candidiasis, rhinitis medicamentosa, atrophic rhinitis, acute of chronic rhinitis and nasal obstructions or abnormalities significant disease history or unstable medical condition use of topical nasal corticosteroid treatment within 2 wks before study, history of hypersensitivity or intolerance to corticosteroids, use of medications that could mask symptoms of rhinitis immediately after study treatment day, use of an experimental drug within 30 days preceding study initiation, previous use of study medications	Washout before study begin with small cup of water, crackers and swatch of wool. Washout period: 1 hr. between medications in Study I and 2 hrs. between medications in Study II	Yes	N/A	Supported by financial grant from AstraZeneca LP	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Bunnag 2003	Method not reported	Yes	NR	Yes	Yes	Yes
Stokes 2004	Method not reported	Yes	NR, only population characteristics of "study groups"reported	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Bunnag 2003	Yes, Yes, Yes, No	No	No	No	Fair	NR/NR/n=364
Stokes 2004	No, Yes, No, No	No	Not clear	NR	Fair-poor	NR/NR/215

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Bunnag 2003	Use of intranasal medications in the 48h preceding the first assessment, oral or systemic corticosteroids in the 2 wks.preceding the first assessment, or depot corticosteroids in the 2 wks.preceding the first assessment, topical decongestants, topical antihistamines and topical cromoglycates prior to the study	Washout before study begin with small cup of water and crackers. Washout period: 30 min. between medications	No	N/A	Aventis Pharma, makers of Nasacort (Triamcinolone)	Yes
Stokes 2004	Use of following medications w/i time period of randomization: intranasal corticosteroids w/i 1 wk oral or systemic corticosteroids w/i 2 wks, an investigational drug w/I 30d depot corticosteroids w/I 8 wks, patients with oral or nasal candidiasis, herpes, acute or chronic sinusitis, severe impairment of nasal breathing, a history of hypersensitivity to corticosteroids or any of the study drugs, or clinically relevant deviations from normal in the general physical examination were also excluded or pregnant or lactating women	Washout before study begin with small cup of water and crackers. Washout period: 30 min. between medications	No	N/A	Aventis Pharma, makers of Nasacort (Triamcinolone)	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Bachert 2002	Method not reported	Yes	NR	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Bachert 2002	No, Yes, No, No	No	Yes	No	Fair	NR/NR/109

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Bachert 2002	Received intranasal corticosteroids within 1 week of randomization, systemic or topical antihistamines, chromones or leukotriene modifiers within 48h of randomization, an investigational drug within 30d of randomization or depot corticosteroids within 8 weeks of randomization, presence of nasal candidiasis, herpes lesions, acute or chronic sinusitis, severe impairment of nasal breathing, clinically relevant deviations from normal in the general physical examination and pregnant or lactating women	Washout before each treatment administration with chewing unsalted crackers, mouth rinsing with water, sniffing swatch of wool cloth. Washout period: 30 min. between medications	No	Yes	Aventis Pharma, makers of Nasacort (Triamcinolone)	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Grubbe 1996	No; sequential	NR	No, beclomethasone group had more males (54% vs 42%) and a lower mean baseline severity score	Yes	Yes	No

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Grubbe 1996	Y/N/N/N	No/No	Unclear	No	Poor	NR/NR/313

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Grubbe 1996	Women that were pregnant, lactating, or of childbearing potential who were not practicing an approved method of birth control; systemic use of a short-acting steroid, a nasal corticosteroid, or nasal cromolyn sodium within 42 days preceding the study baseline period; use of a long-acting steroid within 3 months of the baseline period; use of topical vasoconstrictors more than 3 times/week over the preceding 3 months; initiation of immunotherapy within 1 month of the start of the study; use of medication for another indication that might cause, suppress, or exacerbate the symptoms of allergic rhinitis; a history of habitual abuse of nasal decongestants; hypersensitivity or nonresponse to topoical steroids; sinusitis or an derlying nasal deformity resulting in fixed occlusion of a nostril; rhinitis medicamentosa; significant concomitant illness that would interfere with evaluation of the efficacy and safety of the study medication; evidence of fungal infection in the nose, mouth, or throat; and participation in another investigational study within 30 days of the study screening date	No run-in/5 day washout	No	Yes	NR	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Drouin 1996	Yes	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Drouin 1996	Y/N/N/N	No/No	No; efficacy analysis excluded 40 (9.4%)	No	Fair	NR/NR/427

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Drouin 1996	Patients expected to have clinically significant exacerbation of symptoms due to seasonal aeroallergens by history and skin testing; females pregnant, breast feeding, premenarchal, or not using birth control; required us of inhaled or systemic corticosteroids; upper respiratory tract or sinus infection requiring antibiotic therapy within the previous 2 weeks, dependency upon decongestants; history or evidence of posterior subcapsular cataracts; any significant disorder that could interfere with the study or require treatment that could interfere with the study; use of nasal or ocular corticoids within 2 weeks; inhaled, oral, or intravenous corticoids within 1 month; intramuscular or intra-articular corticoids within 3 months; high potency topical corticoids within one month of initiation of the study	None	No	Yes	Schering-Plough Research Institute	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Mandl 1997	Yes	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Mandl 1997	Y/N/N/N	No/No	No; efficacy analysis excluded 89 (16.2%)	No	Fair	NR/NR/548

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Mandl 1997	Patients expected to have clinically significant exacerbation of symptoms due to seasonal aeroallergens by history and skin testing; females pregnant, breast feeding, premenarchal, or not using birth control; required us of inhaled or systemic corticosteroids; upper respiratory tract or sinus infection requiring antibiotic therapy within the previous 2 weeks, dependency upon decongestants; history or evidence of posterior subcapsular cataracts; any significant disorder that could interfere with the study or require treatment that could interfere with the study; use of nasal or ocular corticoids within 2 weeks; inhaled, oral, or intravenous corticoids within 1 month; intramuscular or intra-articular corticoids within 3 months; high potency topical corticoids within one month of initiation of the study	None	No	Yes	Schering-Plough Research Institute	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Sahay 1980	Unclear; "using a code"	NR	Yes	Yes	n/a-open	n/a-open
McAllen 1980	NR; unclear if randomization used	NR; unclear if randomization used	NR	Yes	Unclear; assessments were conducted using patient self-report (unblinded) and physicians' ratings ("Patients were asked to not reveal details of the physical characteristics of the medication to the physician.")	n/a-open
Svendsen 1989	NR	NR	NR	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Sahay 1980	Y/N/N/N	No/No	Unclear; number of patients analyzed NR	No	Fair	NR/NR/60
McAllen 1980	N/N/N/N	NR	No; excluded 1 patient (3%)	No	Poor	NR/NR/34
Svendsen 1989	N/N/N/N	NR	Unclear; number of patients analyzed NR	Unclear	Poor	NR/NR/23

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Sahay 1980	Pregnancy, respiratory infections requiring antibiotic therapy and nasal obstruction due to nasal polypi; antihistamines use for reasons other than perennial rhinitis; use of test drugs or sodium cromoglycate within 1 month of the start of the trial; use of oral corticosteroids within 3 months of the start of the trial	None	No	Yes	Beclomethasone supplied by Allen and Hansburys Limited; flunisolide supplied by Synetx Pharmaceuticals Limited, Maidenhead	Yes
McAllen 1980	Pregnancy, illnesses in which systemic corticosteroids are contraindicated ; nasal obstruction due to polyps; antihistamine use for reasons other than perennial rhinitis; intranasal steroid or sodium cromoglycate use within the month before admission into the trial; oral steroids within three months of starting the trial	None	No	Yes	Beclomethasone supplied by Allen and Hansburys Limited; flunisolide supplied by Synetx Pharmaceuticals Limited, Maidenhead	Yes
Svendsen 1989	Immunotherapy within 6 months; nasal or systemic corticosteroids within the last 6 weeks; antihistamines; structural abnormalities in the nose; pregnant women; patients receiving medication for treatment of diseases other than bronchial asthma	2-week run-in period during which the patients abstained from all intranasal treatment and practiced completion of the daily record card	No	Yes	NR	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Scadding 1995	NR	NR	NR; only provided baseline characteristics of "efficacy population", which excluded 28% of patients randomized	Yes	Yes	Yes
Al-Mohaimeid 1993	NR	NR	Yes	Yes	Single-blind; unclear who was blinded	Single-blind; unclear who was blinded
Tai 2003	NR	NR	Yes for gender, age, allergy history; no other variables reported	Yes	Blinding NR; QD vs BID treatment	Blinding NR; QD vs BID treatment
van As 1993	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Scadding 1995	Y/N/N/N	No; NR by group	No; excluded 145 patients (28%)	No	Poor	NR/622/516
Al-Mohaimeid 1993	Y/N/N/N	No, No	Yes	No	Fair	NR/NR/120
Tai 2003	Y/N/N/N	None	Yes	No	Fair	NR/NR/24
van As 1993	Y/N/N/N	No, unclear (protocol violations and loss to follow-up patients were group together)	Unclear; number of patients analyzed for efficacy NR	No	Fair	NR/539/466

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Scadding 1995	NR	2-week run-in period for assessment of symptoms	No	Yes	Glaxo Group Research Ltd supplied all medication	Yes
Al-Mohaimeid 1993	Use of oral corticosteroids within the previous 2 months; hyposensitization within the previous 12 months; bacterial, viral or fungal airway infection; severe asthma; planned or actual pregnancy	None	No	Yes	NR	Yes
Tai 2003	Intranasal sodium cromolyn or nedocromil sodium within 6 weeks of initiation of the study; immunotherapy during previous 12 months; nasal surgery during the past 6 weeks; obstructing nasal polyps or significant deviation of the nasal septum; had an infection of the paranasal sinuses or upper or lower respiratory tract in the previous 3 weeks	None	No	Yes	NR	Yes
van As 1993	Oral, inhaled, or intranasal steroids within 1 month or intranasal sodium cromolyn within 2 weeks of initiation of the study	14-day placebo run-in to identify placebo-responders	No	Yes	Glaxo Research Institute	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Bende 2002	Yes	NR	Yes	Yes	Blinding NR	Blinding NR
Bunnag 1984	NR	NR	NR; crossover study	No	Yes; the treatment given to each patient was accomplished on weekly basis by one of the technicians; the physicians who evaluated the results did not know the kind of treatment the patients were being given	No

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Bende 2002	Y/N/N/N	NR	No; excluded 24 (5.5%)	No	Fair	NR/563/438
Bunnag 1984	Y/N/N/N	NR	No, excluded 3 patients (6%)	No	Fair	NR/NR/48

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Bende 2002	History of hypersensitivity to glucocorticoids or antihistamines, asthma requiring systemic or inhaled glucocorticosteroid treatment at doses of > 1,000 ug/day, nasal disorders causing obstruction, or medical conditions or therapies that could interfere with the evaluation of efficacy or safety; use of appropriate contraception	2-week run-in to record symptom scores	No	Yes	Astra Draco AB	Yes
Bunnag 1984	NR	None	No	Yes	Syntex Division, Berli Jucker Co. Ltd supplied the relevant materials	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Haye 1993	NR	NR	Yes	Yes	Yes	Yes
Day 1998	Yes	NR	Yes	Yes	Yes	Yes for budesonide; no for fluticasone

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Haye 1993	Y/N/N/N	Reasons for withdrawal NR	Unclear; reported that only patients who adhered closely to the protocol were included in the efficacy analysis, but number of patients NR	Unclear; reasons for early discontinuation NR	Fair	NR/NR/251
Day 1998	Y/N/N/N	Unclear; reasons for withdrawal NR	No; excluded 41(13.1%)	No	Fair	NR/NR/314

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Haye 1993	Serious or unstable concurrent disease, infection of the paranasal sinuses, upper or lower respiratory tract infections, structural abnormalities (such as large polyps) or had undergone nasal surgery less than six weeks prior to the study; concurrent medication such as oral or inhaled corticosteroids, astemizole, intranasal sodium cromoglycate or intranasal sympathomimetic therapy; pregnant or lactating females	2-week placebo run-in; no washout	No	Yes	NR; 2nd author affiliated with Glaxo Group Research Ltd.	Yes
Day 1998	Systemic or topical intranasal corticosteroid treatment within 2 months before enrollment; required high doses (≥ 1000 ug/day) of inhaled topical steroids for asthma, or if they had other nasal abnormalities possible interfering with efficacy assessments; medications other than the supplied rescue antihistamine possibly interfering with the evaluation of the symptoms of allergic rhinitis; pregnant and nursing women; failure to use effective contraception when applicable; changes in immunotherapy maintenance dose	None	No	Yes	Astra Draco AB	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Klossek 2001	NR	NR	Unknown; baseline characteristics for 22 (23.9%) of 92 patients randomized were NR	Yes	n/a-open	n/a-open
Meltzer 1990	NR	NR	Yes	Yes	Yes	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Klossek 2001	NR	NR	Variable; no for some outcomes and yes for others	NR	Poor	NR/NR/90
Meltzer 1990	Y/N/N/N	None	No; excluded 14 patients (6.5%)	None	Fair	NR/NR/220

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Klossek 2001	Positive skin prick test to pollen and a positive assay for specific IgE, with or without clinical exacerbation during the pollen season; obstructive specific deviation of the nasal septum, nasal polyps, or any other severe concomitant disorders; laboratory abnormalities; known hypersensitivity to test drugs; antihistamines or sodium cromoglycate in the 7 days prior to the inclusion visit; oral or nasal corticosteroids and/or vasoconstrictors in the month prior to the inclusion visit; or corticosteroids or astemizole in the 3 months prior to the inclusion visit; smoking; pregnant women; women likely to become pregnant	None	No	Yes	Aventis	Yes
Meltzer 1990	NR	No run-in/2-week washout of all previous medications for allergic rhinitis	No	Yes	Syntex Laboratories	Yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Meltzer 2005 US	yes	yes	yes	yes	yes	yes

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Meltzer 2005 US	Y/Y/Y/N	None	yes	no	fair	NR/NR/100

Evidence Table 6. Quality assessment of head-to-head trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Meltzer 2005 US	any serious medical condition, including respiratory infection, within two weeks of study enrollment, or a condition associated with anosmia and ageusia within two weeks of study enrollment; use of medication that could mask the symptoms of allergic rhnitis, including nasal steroids, oral or topical nasal decongestants within 1 week of study enrollment; the use os any investigational drug within 30days of study enrollment; or the use of perfume or oral rinse on the study day	10 minutes before receiving each drug, study participants cleansed their mouth with one unsalted cracker and several swallows of water and cleanse the nose by sinffing a swatch of wool	no	yes	a subsidiary of Schering-Plough Corporation	yes

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

Internal Validity

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Chervinsky 2007 US	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind
Meltzer 2007 US	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind
Rosenblut Multicountry 2007	method NR	method NR	yes	yes	don't know; reported as double blind	don't know; reported as double blind
Dahl 2005 Denmark	yes	yes	yes	yes	yes	yes

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

						External Validity
Author, Year, Country	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**
Chervinsky 2007 US	n/n/n/n	no	yes	no	fair	903/NR/663
Meltzer 2007 US	n/n/n/n	no	yes	no	fair	676/NR/471
Rosenblut Multicountry 2007	n/n/n/n	no	yes	yes; 4 pts	fair	984/NR/810
Dahl 2005 Denmark	y/y/y/n	no	yes	no	good	275/NR/262

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Chervinsky 2007 US	History of physical findings of nasal pathology; recent nasal biopsy; nasal trauma; nasal surgery; atrophic rhinitis; rhinitis medicamenntosa; active asthma requiring treatment with corticosteroids or beta agonists, known hypersentivitity to corticosteroids; history of RTI within 14 days of screening visit or development of respiratory infection during baseline; use fo antibiotics within 14 days of screening visit	7-14 day baseline period	no	yes	Altana Pharma	yes
Meltzer 2007 US	Abnormal findings including nasal polyps and nasal tract malformations; rhinitis medicamentosa; evidence of an RTI or significant medical disorder other than AR within 14 days of screening; positive test for hep B, hep C or HIV; active asthma requiring treatment with inhaled or systemitc corticosteroids or routine use of beta agonists; use of prohibited medications during washout periods	7-14 day baseline period	no	yes	Altana Pharma	yes
Rosenblut Multicountry 2007	Any medical condition that could interfere with safety evaluations, including severe nasal obstruction, recent nasal septal or facial surgery; asthma; rhinitis medicamentosa; recent RTI; sinusitis; candida infection of the nose or oropharynx; glaucoma; cataracts; ocular herpes simplex; history of adrenal insufficiency or abnormal ECG or clinical lab test; INS within 4 weeks of screening; corticosteroids within 6 months of screening; other medications that could affect AR.	7-14 day baseline period	no	yes	GlaxoSmithKline R&D	yes
Dahl 2005 Denmark	patients who suffered from asthma and AR because of allergens other than pollen; those receiving chronic treatementwith antiasthma medication or any immunosuppressants and/or immunotherapy over the last 3 years	NR	no	yes	GlaxoSmithKline R&D	yes

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

Author, Year, Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Patient masked?
Gurevich 2005 USA	not clear	not clear	yes	yes	yes	yes
Murphy 2006 USA	not clear	not clear	yes	yes	yes	yes
Stelmach 2005 Brazil	not clear	not clear	yes	yes	yes	yes

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

Author, Year, Country	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating	Number screened/ eligible/ enrolled
Gurevich 2005 USA	y/y/n/n	no	yes	no	fair	NR/NR/26
Murphy 2006 USA	y/n/n/n	no	unclear	no	fair	407/229/229
Stelmach 2005 Brazil	y/n/y/n	no	no	yes	fair	NR/NR/74

Evidence Table 6a. Quality assessment of placebo-controlled trials in patients with PAR

Author, Year, Country	Exclusion criteria	Run-in/washout	Class naïve patients only	Control group standard of care	Funding	Relevance
Gurevich 2005 USA	negative skin test response to a year-round allergen; seasonal allergies; sleep apnea; nasal polyps; deviated septum; atopic diseases other than AR; non-AR; obesity; chronic obstructive pulmonary disease; recent upper and lower airway infection; use of oral or nasal steroids within 30d; and/or use of Betabolckers, tricyclic antidepressants or other medications that are known to affect sleep, rhinitis and daily performance	1-week run-in with saline nasal spray once daily 1 week washout between study arms	no	yes	AstraZeneca	yes
Murphy 2006 USA	any significant chronic disease; any disease or condition that might affect growth; chromosome aberrration; skeletal abnormalities that affect height; evidence of nasal polyps; structural abnormalitites of the nose causing nasal obstruction; a clinically relevant abnoramlity in the physicla examination results; a history of substance abuse, nental illness or retardation; glaucoma or cataraacts, an asthma diagnosis that required treatment with oral or inhaled steroids or leukotriene modifiers; treatment with oral, injectable, or inhaled corticosteroids within 60d of visit1; insufficient AR symptoms to require daily therapy; a history or evidence of abnormal growth;a known gestational age less than 35 weeks; growth velocity below the third percentile at the end of the 6-month baseline period;or any use of medication that could affect growth	none	no	yes	AstraZeneca	yes
Stelmach 2005 Brazil	immunotherapy or hospitalization due to an asthma exacerbation during the previous 6 months, use of oral, injected or inhaled corticosteroids, no respiratory infection during the 4 weeks preceding the study, current use of theophylline or leukotrieneantagonists and history of antiinflammatory drug-induced asthma	2-week run-in with placebo. Only salbutamol and short courses of type-1 antihistamines were allowed as rescue medication	for 3 months prior to study begin	yes	medications and placebo supplied by Farmalab-Chiesi co.	yes

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Day 1990	Randomized, double-blind, parallel, placebo-controlled	Patients aged 6 years and older, with perennial rhinitis for at least 2 years, currently receiving no treatment for rhinitis Exclusion: Pregnancy, tuberculosis, respiratory infection, additional disease, or asthma requiring treatment with corticosteroids	Intranasal budesonide, 200 mean grams twice daily vs placebo Study period: 4 weeks	2 weeks/NR
Fokkens 2002	Randomized, double-blind, placebo-controlled, parallel, multicenter	Children aged 6-16 years with perennial allergic rhinitis for at least 1 year, need for treatment of nasal symptoms, moderate to severe symptom score for blocked nose and at least a mild score for runny nose or sneezing on 4 of 7 days of run-in period	budesonide aqueous nasal spray, 128mcg once daily vs placebo Study period: 6 weeks	NR/NR

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Day 1990	terfenadine, up to two doses 60mg daily	Nasal symptoms scored on daily diary cards	28.6 years 47.4% Male Ethnicity NR	Mean duration of perennial rhinitis: 10.2 years	NR/NR/107
Fokkens 2002	None/NR	Symptoms scores taken daily on dairy cards, evaluation of efficacy questionnaire administered at 1 and 6 weeks, quality of life questionnaires administered twice during study period, use of rescue medication recorded, measurement of nasal eosinophils	10.6 years 68.8% Male Ethnicity NR	Mean Height: 147 cm Mean Weight: 41 kg	NR/NR/202

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment
Day 1990	NR/NR/51	Mean change in symptom scores from baseline to 4 weeks; p-value= B vs placebo: Blocked nose: Allergic rhinitis: B: -0.56 vs placebo: 0.14 Non-allergic rhinitis: B: -0.43 vs placebo: -0.06 Itchy nose: Allergic rhinitis: B: -0.19 vs placebo: -0.16 Non-allergic rhinitis: B: -0.21 vs placebo: 0.01 Runny nose: Allergic rhinitis: B: -0.54 vs placebo: -0.18 Non-allergic rhinitis: B: -0.38 vs placebo: -0.21 Sneezing: Allergic rhinitis: B: -0.35 vs placebo: -0.30 Non-allergic rhinitis: B: -0.44 vs placebo: -0.04 Combined symptoms: Allergic rhinitis: B: -1.62 vs placebo: -0.49 Non-allergic rhinitis: B: -1.46 vs placebo: -0.32	Laboratory tests, patient self-report of adverse events
Fokkens 2002	0/0/202	Change from baseline in nasal symptoms scores and PNIF at 6 weeks: Morning: combined nasal symptom score: B: -1.57 vs placebo: -0.67 blocked nose: B: -0.67 vs placebo: -0.25 runny nose: B: -0.41 vs placebo: -0.12 sneezing: B: -0.45 vs placebo: -0.21	Open questionning at clinic visits

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Day 1990	Nosebleed: Children: B: 0 vs placebo: 1 Adults: B: 4 vs placebo: 1 Sneezing after spray: Children: B: 3 vs placebo: 2 Adults: B: 1 vs placebo: 1 Nasal irritation: Children: B: 5 vs placebo: 2 Adults: B: 4 vs placebo: 3 Nose dryness: Children: B: 1 vs placebo: 2 Adults: B: 1 vs placebo: 1 Coughing: Children: B: 1 vs placebo: 3 Adults: B: 4 v placebo: 0 Headache: Children: B: 7 vs placebo: 8 Adults: B: 8 vs placebo: 5	NR;NR	
Fokkens 2002	No of adverse events reported: B: 75 vs placebo: 73 Most frequent adverse events: pharyngitis: B: 9 vs placebo: 7 respiratory infection: B: 7 vs placebo: 7 viral infection: B; & vs placebo: 6 coughing: B: 7 vs placebo: 4 blood-tinged secretion/nose bleeds: B: 4 vs placebo: 6	0;0	

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Hill 1978	Randomized, double-blind, cross-over, placebo-controlled single-center	Children aged 7-17 years, chronic mouth-breathers with gross hypertropy of nasal mucosa and excessive rhinorrhea, failing to respond to antihistamines and adrengic drugs	Intranasal beclomethasone dipropionate, 300 mg/day vs placebo Study period: NR	NR/NR
Nayak 1998	Double-blind, placebo-controlled multicenter	Children aged 6-12 years with allergic rhinitis, males and premenarcheal females Exclusion: clinically relelvant deviation from normal medical or lab parameters, intolerance to corticosteroid therapy, any medical condition capable of altering pharmokineti	triaminolone acetonide aqueous nasal spray 220g once daily vs 440g once daily Study period: 6 weeks	NR/NR

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Hill 1978	No drugs used for rhinitis allowed during study period	Daily symptom diary results recorded at clinic visits	7-17 years 50% Female Ethnicity NR	Associated recurrent asthma: 12/22 Evidence of marked systemic allergy to house dust mite and/or rye grass	NR/NR/22
Nayak 1998	NR/NR	Adrenocortical function assessed from plasma cortisol levels before treatment, and 30 and 60 minutes after treatment, samples for pharmacokinetic evaluation taken before treatment at 30, 60, 90 minutes, and at 6 hours after treatment, daily diary cards	9.5 years Gender NR Caucasian: 84%	NR	NR/NR/80

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment
Hill 1978	0/0/22	Number of children with response: Nasal symptoms: Improved score: 19 Unchanged score: 0 Worse score: 3 Nasal signs: Improved score: 15 Unchanged score: 7 Worse score: 0 Eye symptoms: Improved score: 13 Unchanged score: 4 Worse score: 5	Patient daily symptom diary
Nayak 1998	1/0/79	Mean differences in plasma cortisol levels between baseline at week 6: 0 hrs: TAA 220g: -1.40 TAA 440g: -0.19 Placebo: 0.67 30 min: TAA 220g: 0.04 TAA 440g: 0.29 Placebo: -0.19 60 min: TAA 220g: -0.57 TAA 440g: 0.56 Placebo: -0.94	Patient report

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Hill 1978	None reported	0;0	
Nayak 1998	Percentage of patients reporting adverse events: TAA 220g/d: 54% TAA 440g/d: 42% Placebo: 35%	0;0	

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Neuman 1978	Double-blind, crossover	Children aged 9-18 years, with perennial allergic rhinitis and daily symptoms of sneezing, rhinorrhoea and nasal obstruction for at least 5 years	beclomethasone dipropionate 50g inhaled in each nostril, 4 times daily Study period: 6 weeks	NR/NR
Ngamphaiboon 1997 Thailand	Randomized double-blind, single dose, placebo-controlled, parallel multicenter	Children aged 5-11 years with moc	fluticasone propionate 100mcg vs placebo Study period: 4 weeks, with 2 weeks additional followup	NR/ 2 week washout between treatments
Sarsfield 1979	Randomized, double-blind, crossover study	Children with perennial arthritis	Nasal flunisolide vs placebo Study period: 2 months Then 17 patients responding well with flucisolide continued treatment for additional 6 month, open period	NR/NR

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Neuman 1978	NR	Daily diary cards, weekly clinical visits for physical and assessment of nose and throat secretions	13.8 years 46.6 Male Ethnicity NR	Family history of atophy: 24/30 Clinical hypersensitivity to food/drugs: 7/30 Maxilliary sinusitis: 12/30	NR/NR/30
Ngamphaiboon 1997 Thailand	clemastine tablets (1mg) or syrup (0.5mg/5 mL) used when symptoms deemed intolerable of rhinitus during treatment periods	Assessments taken ever 2 weeks, variables: nasal and symptoms scored by investigator, overall physical examination at first and final days of treatment periods, nasal and ocular symptoms scored by patient on daily diary cards, clemastine use, blood sample	9.01 years 14.6% Female 11.8% Oriental 38.2% Asian	Mean height, cm: placebo: 131.92, fluticasone: 129.87 Mean weight, kg: placebo: 31.13 , fluticasone: 27.39	NR/127/106
Sarsfield 1979	Sodium cromoglycate inhalations (n=1) beclomethasone dipropionate pulmonary aerosol (n=4) corticosteroid creams (n=3)	Patients completed weekly diary cards, monthly clinical assessments and end-of-trials preferences	12 years 77.7% Male Ethnicity NR	Mean duration of rhinitis: 7 years Family history of disease: 67% One or more allergic problems: 70%	NR/NR/27

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment
Neuman 1978	NR/NR/NR	Mean daily nasal symptom scores: Week 1: BD: 1.5 vs placebo: 2.75 Week 2: BD: 0.5 vs placebo: 3.0 Week 3: BD: 0.5 vs placebo: 3.0 Week 4: BD: 1.0 vs placebo: 2.5 Week 5: BD: 0.75 vs placebo: 2.75 Week 6: BD: 0.25 vs placebo: 3.0	Patient outcome, self-report
Ngamphaiboon 1997 Thailand	0/0/106	Mean total symptom scores: At 2 weeks: fluticasone propionate: 4.4 (p < 0.01) vs placebo: 6.09 At 4 weeks: fluticasone propionate: 3.96 (p < 0.01) vs placebo: 5.39	Inquiry of patient by nvestigator at each assessment
Sarsfield 1979	1/0/26	Mean changes in scores from baseline: First 4 weeks of flunisolide vs Second 4 weeks of placebo: Sneezing: F: -1.57 vs placebo: -0.64 Stuffiness: F: -1.36 vs placebo: -0.64 Runny nose: F: +0.71 vs placebo: +0.57 Nose-blowing: F: +1.14 vs placebo	Patient outcome, self-report

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Neuman 1978	None Reported	NR;NR	
Ngamphaiboon 1997 Thailand	None reported	0; 0	
Sarsfield 1979	Most common adverse events reported: transient nasal stinging After 6 month open-period, measurements of 0900 blood cortisol concentrations found no effect.	1;1	

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Shore 1976	Randomized, double-blind, placebo-controlled, cross-over single-center	Children aged 4-12 years, with perennial allergic rhinitis for over 1 year, failure to respond to sodium cromoglycate insufflation and hyposensitization, pretreatment observation at study clinic for at least 6 months, symptomatic at screening, radiological studies excluding abnormalities causing obstruction, inadequate previous response to treatment	Intranasal beclomethasone vs placebo Study period: 4 months	NR/ 3 week washout between treatments
Storms 1991	Randomized, double-blind, placebo-controlled, parallel Multi-center	Patients aged 12-65 years, with perennial allergic rhinitis for at least 2 years, poor response to antihistamines and/or decongestants or immunotherapy, postive skin prick test for at least allergin Exclusion: pregnancy or lactation, use of nasal cromolyn	triamcinolone acetonide nasal spray, 110g vs 220g vs 440g once daily vs placebo Study period: 12 weeks	NR/NR
Todd 1983	Randomized, double-blind, cross-over	Children with perennial rhinitis	fluisolide nasal spray 50g three times daily, vs placebo Study period: 8 weeks	NR/NR

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Shore 1976	Patients allowed to continue usual antihistamine decongestant therapy	Daily symptom diary results recorded at clinic visits	8 years 78.2% Male Ethnicity NR	Allergy to grass extract: 36% Allergy to animal danders: 12% Asthma: 78% Eczema: 21% Ocular allergy: 19%	NR/NR/46
Storms 1991	Oral backup medication permitted	Nasal stiffiness, discharge, sneezing, itching and nasal index	25 years 67% Male White: 89.8%, Black: 6.5%, Other: 3.6%	NR	NR/NR/305
Todd 1983	NR	Clinical assessments taken at baseline, 4 weeks and 8 weeks, assessing severity of symptoms scores	8.3 years 60.9% Male Ethnicity NR	Positive reaction to at least 1 common allergin: 53% Positive reaction to house-dust mite allergy: 90% family history: 64%	NR/NR/NR

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Number withdrawn/ lost to fu/analyzed	Outcomes	Method of adverse effects assessment
Shore 1976	2/0/44	Results record cards of beclometasone: Success: 38 (86%) Failure: 6	Patient daily symptom diary
Storms 1991	0/0/305	Mean Changes from Baseline in Symptoms Scores: Week 6: Nasal Stuffiness: 110mcg: -0.8 vs 220mcg: -1.1 vs 440mcg: -1.25 vs placebo: -0.7 Nasal Discharge: 110mcg: -0.9 vs 220mcg: -1.25 vs 440mcg: -1.2 vs placebo: -0.7 Sneezing:110mcg: -1.0 vs 220mcg: -1.	Patient outcome, self-report
Todd 1983	NR/NR/64	Changes in symptomatolgy from baseline to 8 weeks- p-value of difference between treatment and placebo: Sneezing: p=0.025 Stuffiness: p= 0.032 Runny nose: p= 0.239 Nose-blowing: p= 0.330 Post-nasal drip: p= 0.169 Epistaxis: p= 0.195	Indirect questionning at clinic visits

Evidence Table 7. Placebo-controlled trials in children with PAR

Author Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Shore 1976	None reported	2;0	
Storms 1991	Adverse events reported: Headache: T200: 16% vs T400: 18% vs T800: 21% vs placebo: 18% Upper respiratory infection: T200: 4% vs T400: 5% vs T800: 7% vs placebo: 13% Epistaxis: T200: 3% vs T400: 3% vs T800: 4% vs placebo: 9% Throat discomfort: T200: 1%	0;0	
Todd 1983	Nasal irritation: F: 12 vs placebo: 10 Eyes running: F: 3 vs placebo: 1 Nose bleed: F: 1 vs placebo: 1 Itch: F: 2 vs placebo: 0 Nausea: F: 1 vs placebo: 0 Headache: F: 2 vs pacebo: 2 Sleepy: F: 0 vs placebo: 1 Rash: F: 0 vs placebo: 1	NR;NR	

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

	Internal Validity							
Author, Year, Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Day 1990	Method not reported	NR	Yes	Yes	Yes	Yes	Yes	No, No, Yes, No
Fokkens 2002	Method not reported	NR	Some	Yes	Yes	Yes	Yes	No, No, No, No
Hill 1978	Method not reported	NR	NR	Yes	Yes	Yes	Yes	No, Yes, No, No

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

					External Validity		
Author, Year, Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Day 1990	No	Yes	No	Fair	NR/NR/107 adults and children	Pregnancy, tuberculosis, respiratory infection, additional nasal disease or asthma requiring treatment with corticosteroids	2-week baseline period where patients recorded symptoms and received only terfenadine (60mg up to two tablets per day
Fokkens 2002	No	Yes	No	Fair	NR/NR/202	Polllen allergy in season, upper respiratory infection within 2wks before screening, rhinitis medicamentosa or structural abnormalities symptomatice enough to cause significant nasal obstruction, unstable asthma, immunotherapy not on constant maintenance dose, any other significant diseases, systemic corticosteroid therapy within 2 months, extensive application of topical cutaneous steroids, topical nasal steroids within one month before screening, other medication possibly interfering: antihistamines within 3 days, cromoglycate within 2 wks, astemizole within 1 month before screening	1-week baseline period in which efficacy variables were measured twice daily
Hill 1978	No	Yes	No	Fair	NR/NR/22	None reported	No

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

Author, Year, Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Day 1990	No	N/A	One author is from AB Draco, Lund, Sweden	Yes
Fokkens 2002	No	N/A	Financial support from AstraZeneca R&D, Lund Sweden	Yes
Hill 1978	No	N/A	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

	Internal Validity							
Author, Year, Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Nayak 1998 USA	NR	yes	yes	yes	yes	NR	yes	yes, no, yes, no
Neuman 1978 Israel	NR	NR	NR	yes	yes	NR	yes	yes, yes, no, no

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

					External Validity		
Author, Year, Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Nayak 1998 USA	no	yes	no	fair	NR/NR/80	Any clinically relevant deviation from normal medical or laboratory parameters, an intolerance to corticosteroid therapy, any medical condition capable of althering the pharmacokintics of the drup, acute infetiors sinusitis, underlying nasal pathology resulting in occlusion of a nostril, visible evidence of fungal infectionn of the nose, throat, or mouth, or an initial morning plasma cortisol level outside the range of 5 to 20 mcg/dl. Also patients treated with systemic corticosteroids within 90d, oral corticosteroids for more than 10d within the past year, or if they participated in any investigational drug study within 60d or any previous study with triamcinolone aquesous nasal spray.	no
Neuman 1978 Israel	no	not clear	no	poor	NR/NR/30	NR	no

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

Author, Year, Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Nayak 1998 USA	no	yes	Supported in part by Rhone-Poulenc rore Pharaceuticals, Inc.	yes
Neuman 1978 Israel	no	yes	NR	yes

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

	Internal Validity							
Author, Year, Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Ngamphaiboon 1997	Method not reported	NR	Yes	Yes	Yes	NR	Yes	No, No, Yes, No
Sarsfield 1979 UK	NR	NR	NR	NR	yes	NR	yes	Yes, yes, no, no
Shore 1977	Method not reported	NR	NR	Yes	Yes	Yes	Yes	Yes, Yes, No, No

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

					External Validity		
Author, Year, Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Ngamphaiboon 1997	No	Yes	No	Fair	NR/NR/106	Physical obstruction in the nose, concurrent diseases that would affect their ability to participate safely and fully in the study, hypersensitivity to any corticosteroid, use of any steroid, sodium cromoglycate or nedocromil sodium 2 weeks before enrollment, oral astemizole 6 weeks before the study, hyposensitization treatment during the previous 12 months, or concurrent infection of paranasal sinuses or upper or lower respiratory tract.	No
Sarsfield 1979 UK	no	yes	no	fair to poor	NR/NR/27	NR	Not reported
Shore 1977	No	Yes	No	Fair	NR/NR/46	None reported	1-week washout between cross-over

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

Author, Year, Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Ngamphaiboon 1997	No	N/A	Financial support from Glaxo Thailand	Yes
Sarsfield 1979 UK	no	yes	NR	yes
Shore 1977	No	N/A	NR	Yes

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

	Internal Validity							
Author, Year, Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Storms 1996	Method not reported	NR	no	yes	yes	yes	yes	yes, no, no, no
Todd 1983	Method not reported	NR	NR	yes	yes	yes	yes	No, yes, no, no

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

					External Validity		
Author, Year, Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Storms 1996	no	yes	no	fair	NR/NR/137	Any clinical deviation from normal medical or lab parameters, nasal candiasis, acute sinusitis, or a history of hypersensitivity to corticosteroids Any of the following conditions: treatment with nasal, inhaled or systemic corticosteroids within 42 days prior to the study, nasal cromolyn sodium within 14d, medication that might produce or relieve symptoms of allergic rhinitis, or an investigational drug within 90d, initiation of immunotherapy within 30d or participation in any previous Triamcinolone trials.	no
Todd 1983	no	no	No	fair	NR/NR/64	None reported	No

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

Author, Year, Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Storms 1996	no	N/A	funded by Rhone-Poulenc Rorer Pharmaceuticals	yes
Todd 1983	No	N/A	Materials supplied by Syntex Pharmaceuticals Ltd.	yes

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

	Internal Validity							
Author, Year, Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**
Welch 1991	Method not reported	NR	yes	yes	yes	yes	yes	no, no, no, no

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

					External Validity		
Author, Year, Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Welch 1991	no	no	NR	fair	NR/NR/210	Use of oral or parenteral corticosteroids within 60d prior to study, or long-acting depot steroids within 6 months, use of nasal corticosteroids or nasal cromolyn within 30d of the study, any evidence of infection, sinusitis, otitis media, nasal polyps or any fixed anatomical abnormality and lack of stabilization with immunotherapy	Baseline period of 6-10d, no rhinitis medication was allowed during the last 5d

Evidence Table 8. Quality assessment of placebo-controlled trials in children with PAR

Author, Year, Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Welch 1991	no	N/A	Supported by a grant from Rhone-Poulenc Rorer Pharmaceuticals	yes

Evidence Table 9. Trials in patients with non-allergic rhinitis

Author Year	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period	Allowed other medications/ interventions
Lundblad 2001	Randomized, double-blind, placebo-controlled Multi-center	Patients aged 18-82 years with perennial non-allergic rhinitis, unspecific rhinitis symptoms Exclusion: Positive skin prick tests, intolerance to aspirin or non-steroidal anti-inflammatory drugs, structural abnormalilties, nasal polyps	mometasone furoate nasal spray, 200mcg once daily vs placebo Study duration: 11 weeks	NR/NR	Prohibited: topical nasal, ocular or oral decongestants,nasal saline, short and long-acting anti-histamines, nasal atropine or ipratropium bromide, ketotifen, azelastine and intransal or ocular corticosteroids for 1-2 weeks, investigational drugs
Webb 2002	3 randomized, placebo-controlled, double-blind, parallel trials Multi-center	Patients aged >11 years, with perennial rhinitis with or without eosinophilia, negative skin tests to all allergins relevant to geographic region	intranasal fluticasone propionate, 200g daily vs 400g daily vs placebo Study period: 4 weeks	NR/NR	NR

Evidence Table 9. Trials in patients with non-allergic rhinitis

Author Year	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Outcomes
Lundblad 2001	Patient daily diary of symptoms	NR	NR	NR/NR/329	NR/NR/NR	Improvement rates: Patient report PP: MFNS: 69/119 (58%) vs placebo: 62/132 (47%) ITT group: MFNS: 93/167 (56%) vs placebo: 80/162 (49%) Improvement rates: Investigator report PP: MFNS: 74/119 (62%) vs placebo: 61/132 (46%) ITT group: 100/167 (60%) v
Webb 2002	Nasal cosinophild evaluated with 5-point scale, total nasal symptom score (TNSS), patient ratings of symptoms, taken at clinic visits at 2 and 4 weeks	42 years 37% Male 94% Caucasian	Duration of rhinitis: placebo vs F200 vs F400: 1-4 years: 26% vs 23% vs 26% 5-9 years: 20% vs 27% vs 22% 10-14 years: 19% vs 17% vs 19% >15 years: 35% vs 32% vs 33%	NR/NR/983	<2%/NR/95%	Improvement in TNSS both F200g and 400g, each week vs placebo: p<0.002

Evidence Table 9. Trials in patients with non-allergic rhinitis

Author Year	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Lundblad 2001	Patient self-report	Adverse events reported: Upper respiratory infection: MFNS: 27.2% vs placebo: 30.2% Headache: MFNS: 27.2% vs placebo: 27.2% Epistaxis: MFNS: 12.4% vs placebo: 5.6% Sore throat: MFNS: 11.2% vs placebo: 8%	NR;NR
Webb 2002	Patient outcome, self-report	Epistaxis: F200g: 1 vs F400g: 2	0;5%

Evidence Table 10. Quality assessment of trials in patients with non-allergic rhinitis

	Internal Validity										
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**	**Patient masked?**	**Reporting of attrition, crossovers, adherence, and contamination**	**Loss to follow-up: differential/ high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**
Lundblad 2001 Sweden, Norway, Finland, Denmark	NR	NR	NR	Yes	Yes	NR	Yes	Yes, No, No, No	Not clear	yes	No
Webb 2002 USA	NR	NR	Yes	Yes	Yes	NR	Yes	Yes, No, No, No	No	Yes	No

Evidence Table 10. Quality assessment of trials in patients with non-allergic rhinitis

		External Validity						
Author, Year Country	**Quality rating**	**Number screened/eligible/ enrolled**	**Exclusion criteria**	**Run-in/ Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
Lundblad 2001 Sweden, Norway, Finland, Denmark	Fair	NR/NR/329	Aspirin intolerance or non-steroidal anti-inflammatory drugs. Significant septal deviations or other structural deformities or nasal polyps.	2-week screening period	No	Yes	NR	Yes
Webb 2002 USA	Fair	NR/NR/983	Use of other rhinitis medication	7-day screening period	No	Yes	Supported in part by SmithKline Beecham Corporation doing business as GlaxoSmith Kline	Yes

Evidence Table 11. Observational studies

Author, year Country	Data source	Prospective Retrospective Unclear	Exposure period	Mean duration of follow-up
Derby, 2000 UK	UK-based General Practice Research Database	Retrospective	1991-1996	Estimated from graph, person years of follow up by age and treatment cohort Intranasal: <20y: 21,000 20-39y: 31,500 40-59y: 27,000 60+y: 10,500 Unexposed: <20y: 25,000 20-39y: 34,000 40-59y: 30,000 60+y: 11,500
Koepke, 1997 USA	Open-label continuation of 4-week RCT	Prospective	12 months, specific dates not reported	94.2% completed 3 months 83.6% completed 6 months 62% completed 12 months

Evidence Table 11. Observational studies

Author, year Country	Interventions Mean dose	Population	Age Gender Ethnicity	Exposed Eligible Selected
Derby, 2000 UK	Exposure to intranasal corticosteroids only (beclomethasone, fluticasone, budesonide) or oral corticosteroids only or not exposed to any corticosteroids	Less than 70 years old in 1993 without a history of asthma or chronic obstructive pulmonary disease (except for oral steroids cohort) **total study population:** 286,078 **intranasal corticosteroid users:** 88,301, about 70% used beclomethasone only **oral corticosteroid users:** 98,901, 41% had no previous evidence of either asthma or COPD **unexposed cohort:** 98,876	**Intranasal corticosteroid users:** mean age NR, 25% aged 50 or older 56% female ethnicity NR **unexposed cohort:** mean age NR, 25% aged 50 or older 51% female ethnicity NR **oral corticosteroid users:** mean age NR, 50% aged 50 or older 56% female ethnicity NR	NR, NR, n=286,078
Koepke, 1997 USA	220mcg triamcinolone aqueous/day with an option to reduce to 110mcg triamcinolone/day if symptoms were controlled	Adolescent and adult patients with at least 2 year history of perennial allergic rhinitis	Mean age: 31 years (range, 11-59 years) 37% female and 64% male 98% white	NR, 178, n=172

Evidence Table 11. Observational studies

Author, year Country	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Derby, 2000 UK	N/A	N/A
Koepke, 1997 USA	34/5/172	Mean changes in visual analog scale scores from the start of double-blind treatment Mean Improvement in symptoms compared to the double-blind baseline mean (estimated from figure), all p<0.0001 1 month: 2.8 2 months: 3.4 3-5 months: 3.5 6-7 months: 3.65 8-9 months: 3.3 10-11 months: 3.7 12-13 months: 4.1

Evidence Table 11. Observational studies

Author, year Country	Safety outcomes	Comments
Derby, 2000 UK	**Number of cases of cataract** Intranasal corticosteroid users: 217 in 208,753 person-years Beclomethasone only: 140 in 140,831 person-years Unexposed cohort: 213 in 206,560 person-years Oral corticosteroid users: 629 in 289,371 person-years Subjects without asthma: 274 in 91,064 person-years **Incidence rate/1000 person-years (95% CI)** Intranasal corticosteroid users: 1.0 (0.9-1.2) Beclomethasone only: 0.9 (0.7-1.0) Unexposed cohort: 1.0 (0.9-1.1) Oral corticosteroid users: 2.2 (2.0-2.3) Subjects without asthma: 3.0 (2.7-3.4) **Relative Risk of cataract (95% CI)** Intranasal corticosteroid users: 1.0 (0.8-1.2) Beclomethasone only: 1.0 (0.8-1.2) Unexposed cohort: reference Oral corticosteroid users: 2.1 (1.8-2.5) Subjects without asthma: 2.9 (2.4-3.5)	Funded by GlaxoWellcome Inc.
Koepke, 1997 USA	Withdrawals due to AE: 8 (5%) Withdrawals due to treatment-related AE: 4 (2.5%) **Overall AE:** 133 (77.3%) Headache: 38 (22.1%) Epistaxis: 31 (18%) Pharyngitis: 55 (32.0%) Rhinitis: 49 (28.5%) Cough: 14 (8.1%) Sinusitis: 27 (15.7%) **AE due to topical effects:** Nasal irritation 4 (2.3%), nasosinus congestion 2 (1.2%), Throat discomfort and dry mucous membranes 0%, sneezing 1 (0.6%), and epistaxis 22 (12.8%)	Funded in part by Rhone-Poulenc Rorer Pharmaceuticals, Inc.

Evidence Table 11. Observational studies

Author, year Country	Data source	Prospective Retrospective Unclear	Exposure period	Mean duration of follow-up
Mansfield, 2002 USA	Pediatric clinical records	Retrospective	12 months to 91 months, specific dates not reported	36 months
Moller, 2003 Sweden	Six Swedish pediatric clinics, open, non-controlled trial	Prospective, 24-month observation	NR	73 children completed 1 year and 33-37 children completed 24 months
Lange, 2005 Germany	study	prospective	2003 grass pollen season	mean NR 4-week study

Evidence Table 11. Observational studies

Author, year Country	Interventions Mean dose	Population	Age Gender Ethnicity	Exposed Eligible Selected
Mansfield, 2002 USA	beclomethasone aqueous 168mcg twice daily with occasional dosing of 168mcg once daily	Children with perennial allergic rhinitis with seasonal exacerbations children with concomitant asthma or allergic dermatitis and those who had used systemic or topical steroids were excluded	Mean age: 70 months (range, 24-117months) 20 girls (33.3%) and 40 boys (67.7%) 75% Mexican-American	NR, NR, n=60
Moller, 2003 Sweden	budesonide in a pressurized metered dose inhaler, starting dose 400mcg/day and adjusted to max. 600mcg/day as needed. In the second year reductions to 200mcg were allowed. After 18 months patients were transferred to budesonide aqueous at daily doses of 200-400mcg/day	Children with perennial allergic rhinitis children who had used oral steroids in previous 3 months were excluded	**First year** mean age: 10.8 years, range (5-15 years) 22 girls (28%) **Second year** mean age: 10.7 years, range (6-15 years) 10 girls (21%) Ethnicity not reported	NR, NR, n=78
Lange, 2005 Germany	200mcg Mometasone furoate once daily vs. 200 mcg levocabastine hydrochloride twice daily vs. 5.6mg disodium cromoglycate 4 times daily	seasonal allergic rhinitis history of 2 years or longer, sensitization to grass pollen and age 18-65 years	mean age: 34.6 years 59.4% female NR	NR NR n=123

Evidence Table 11. Observational studies

Author, year Country	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Mansfield, 2002 USA	N/A	NR
Moller, 2003 Sweden	9 subjects withdrawn (5 in year 1 and 4 in year 2) Analyzed in year one: 73 and in year two: 33-37	Severity and duration of all daily nasal symptoms (4-point scale): reduced compared to pre-treatment, p<0.0001 (no specific data reported) Investigators' rhinoscopy assessments improved compared to pre-treatment at all visits, p<0.05 Patient-rated overall efficacy of treatment: good or very good by 89% of patients (after the first year) Physician-rated overall efficacy of treatment: good or very good by 91% of patients (after the first year) Eye symptoms scores: 0.38 at entry and 0.26 after 12 months of treatment, p<0.05
Lange, 2005 Germany	3 withdrawn 0 lost to follow up n=123	Mometasone vs. levocabastine vs. disodium cromoglycate Total nasal symptom scores (TNSS) Total symptom scores (TSS) All-day TNSS, 0.65 vs. 0.96 vs. 1.07 Daytime TNSS 0.69 vs. 0.99 vs. 1.14 Nighttime TNSS 0.60 vs. 0.94 vs. 1.00 All-day TSS 0.68 vs. 0.97 vs. 1.04 Daytime TSS 0.72 vs. 1.00 vs. 1.11 Nighttime TSS 0.63 vs. 0.95 vs. .98 Days free of nasal symptoms, % 14.46 vs. 5.98 vs. 5.04 Days free of all symptoms, % 10.22 vs. 4.57 vs. 4.83

Evidence Table 11. Observational studies

Author, year Country	Safety outcomes	Comments
Mansfield, 2002 USA	Growth measured by stadiometry Measured mean height at entry: 149.9cm Measured mean height at 12 months: 154.8cm Mean difference in the comparison between the observed and expected heights: at entry +3.8cm and at 12 months +3.6cm	Funding sources NR
Moller, 2003 Sweden	**Growth measured by stadiometry** Measured mean height at entry: 149.9cm Measured mean height at 12 months: 154.8cm Mean difference in the comparison between the observed and expected heights: at entry +3.8cm and at 12 months +3.6cm Mean height of predicted at entry: 102.5% and after 12 months: 102.2% (NSD) Subpopulation treated for two years: Measured mean height at entry: 148.9cm Measured mean height at 24 months (n=35): 159.3cm Mean difference in the comparison between the observed and expected heights (n=33): at entry +2.9cm and at 24 months +2.9cm (NSD) Mean height of predicted at entry: 102.1% and after 12 months (n=37): 101.9% (NSD)	One author is from AstraZeneca R&D
Lange, 2005 Germany	Mometasone vs. Levocabastine vs. Disodium Cromoglycate Patients with less than one AE 18 vs. 18 vs. 20 All EAs 40 vs. 35 vs. 42 Headache or migraine 18 vs. 11 vs. 17 Infections or colds 6 vs. 7 vs. 5 Local irritation or complaints in nose or pharynx 3 vs. 2 vs. 5 GIT 3 vs. 1 vs. 4 Fatigue or sleepiness 1 vs. 4 vs. 0 Vertigo 3 vs. 0 vs. 0 Cardiovascular 3 vs. 2 vs. 2 Skin 1 vs. 1 vs. 2 Musculoskeletal 1 vs. 1 vs. 2	

Evidence Table 11. Observational studies

Author, year Country	Data source	Prospective Retrospective Unclear	Exposure period	Mean duration of follow-up
Pitsios, 2006 Greece	study	prospective	Spring 2002	mean NR treatment starting 2-4 weeks before pollen season and continuing for up to 4 months

Evidence Table 11. Observational studies

Author, year Country	Interventions Mean dose	Population	Age Gender Ethnicity	Exposed Eligible Selected
Pitsios, 2006 Greece	400mcg Mometasone furorate once daily	seasonal allergic rhinitis history of 2 years or longer, sensitization to local pollen and age older than 12 years	mean age: 28.9 years 42.6% female NR	NR NR n=61

Evidence Table 11. Observational studies

Author, year Country	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Pitsios, 2006	none	Mometasone vs. Nedocromil sodium
Greece	none	% of days with minimal symptoms as measured using total nasal symptom scores, 86% vs. 64%,
	n=61	p<0.001
		Use of rescue medicine, % of total study days, 15.6% vs. 18.3%, p=0.01
		Mean daily total symptom score, 1.4 vs. 2.89, p<0.001

Evidence Table 11. Observational studies

Author, year Country	Safety outcomes	Comments
Pitsios, 2006 Greece	Mometasone vs. Nedocromil sodium, all NSD Fever, 0 vs. 0% headache, 3 vs. 4% somnolence, 3 vs. 0% insomnia, 6 vs. 4% burning nose, 13 vs. 19% epistaxis, 6 vs. 4% bad taste, 9 vs. 7%	

Evidence Table 11. Observational studies

Author, year Country	Data source	Prospective Retrospective Unclear	Exposure period	Mean duration of follow-up
Baysoy, 2007 Turkey	study	prospective	NR	NR 2 month study
Weber, 2006 USA	study	prospective	1994-95	NR one year study duration of treatment <2 months, 43 (10.9%) >2 months and <6 months, 57 (14.4%) >6 months, 296 (74.7%)

Evidence Table 11. Observational studies

Author, year Country	Interventions Mean dose	Population	Age Gender Ethnicity	Exposed Eligible Selected
Baysoy, 2007 Turkey	100mcg/day fluticasone proprionate for children<12 years and 200mcg/day for children > 12 years	allergic rhinitis	mean age: 7.6 48% female NR	NR NR n=196
Weber, 2006 USA	Triamcinolone actonide hydrofluoroalkane-134a (propelled) 2 week run-in with 220mcg once daily Adjustments as needed to 440mcg or 110mcg once daily Doses were standardized to 440mcg at approx. 4 months	perennial allergic rhinitis	mean age: 31.9 years 47.2% female 92.4% white	NR NR n=396 in safety population

Evidence Table 11. Observational studies

Author, year Country	Withdrawn Lost to fu Analyzed	Effectiveness outcomes
Baysoy, 2007 Turkey	108 withdrawn or lost to follow up n=88	NA
Weber, 2006 USA	140 (35.3%) withdrawn 5.8% lost to FU n=396	NA

Evidence Table 11. Observational studies

Author, year Country	Safety outcomes	Comments
Baysoy, 2007 Turkey	pre-treatment nasal S. aureus carriage vs. post treatmentnasal S. aureus carriage, NSD between groups treatment vs. control group pre-treatment, 7 (18.4%) vs. 10 (20.0%) post-treatment, 6 (15.7%) vs. 10 (20%)	
Weber, 2006 USA	AEs; Number of patients (%;n = 396) Pharyngitis 143 (36.1) Rhinitis 114 (28.8) Application-site reaction 105 (26.5) Headache 101 (25.5) Epistaxis 86 (21.7) Sinusitis 66 (16.7) Injury accident 36 (9.1) Flu syndrome 35 (8.8) Increased cough 30 (7.6) Pain 25 (6.3) Pain back 23 (5.8) Reaction unevaluable 23 (5.8) Tooth discomfort 21 (5.3) Dyspepsia 20 (5.1) Bronchitis 20 (5.1)	34 (8.6%) withdrew due to AE

Evidence Table 12. Quality assessment of observational studies

Author, year	Non-biased selection?	Low overall loss to follow-up?	Outcomes pre-specified and defined?	techniques adequately described?	Non-biased and accurate ascertainment methods?	Statistical analysis of potential confounders?
Derby, 2000	yes	N/A	yes	yes	yes	yes
Moller, 2003	not clear	yes	yes	yes	not clear	partially
Mansfield, 2002	not clear	N/A	yes	yes	not clear	yes
Koepke, 1997	yes	no	yes	yes	not clear	not clear
Lange, 2005	yes	yes	yes	yes	yes	yes
Pitsios, 2006	not clear	yes	yes	yes	not clear	not clear
Baysoy, 2007	not clear	no	yes	yes	not clear	not clear
Weber, 2006	yes	no	yes	yes	not clear	not clear

Evidence Table 12. Quality assessment of observational studies

Author, year	Adequate duration of follow-up?	Adequate sample size?	Overall quality assessment
Derby, 2000	N/A	yes	fair-retrospective study
Moller, 2003	yes	yes	fair
Mansfield, 2002	N/A	yes	fair-retrospective study
Koepke, 1997	yes	yes	fair
Lange, 2005	not clear	yes	fair
Pitsios, 2006	not clear	yes	fair
Baysoy, 2007	yes	yes	fair
Weber, 2006	yes	yes	fair

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Schenkel 2000	Randomized, double-blind, placebo-controlled multicenter	Children with perennial allergic arthritis no greater than stage 1 on the Tanner Classification of Sexual Maturity, height between 5th-95th percentile Exclusion criteria: asthma requiring chronic use of inhaled corticosteroids for asthma for >2 months, history/presence of abnormal growth or malnutrition, history of multiple drug allergies, allergy to corticosteroids, posterior subcapsular cataracts or nasal structural abnormailites, upper respiriatory infection, sinus infection within 1 week before study	mometasone furoate aqueous nasal spray (MFNS), 100 mean grams once daily vs placebo Study period: 12 months	NR/NR
Skoner 2000	Randomized, double-blind, twice daily dose, placebo-controlled, parallel	Prepuertal children, aged 6-9 years with perennial allergic rhinitis, baseline heights between 5th-95th percentile, skeletal age within 2 years of chronological age	intranasal beclomethasone dipropionate 168mcg vs placebo Study period: 1 year	NR/NR

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Schenkel 2000	Treatment with immunotherapy if patient on a stable schedule for at least 1 month before screening, 1-2 courses oral prenisone lasting no > 7 days, oral corticosteroids, low-potency dermatologic corticosteroids, nonsteroidal allergy preparations	Cosyntropin stimulation testing performed in half of centers at 6 and 12 months, vital signs taken at each visit, clinical lab determinations taken at baseline, week 26 and endpoint, height measured at 4, 8, 12, 26, 39 and 52 weeks	6.3 years 67.3% Male Ethnicity NR	Asthma: MFNS: 32.6% vs placebo: 26.5% Comorbid SAR: MFNS: 79.5% vs placebo: 73.4% Mean body weight: MFNS: 54.5 vs placebo: 55.2 Mean height: MFNS: 120.2cm vs placebo: 120.9cm	NR/NR/98
Skoner 2000	NR/NR	Height measured with stadiometer at 1,2, 4,6, 8, 10 and 12 months	NR	NR	NR/NR/100

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment
Schenkel 2000	14/16/82	Mean Increase in Height after 12 months of treatment: Age 3-5y: MFNS: 7.65 cm vs placebo: 7.26 cm Age 6-9y: MFNS: 6.67 cm vs placebo: 6.0cm Female: MFNS: 6.73cm vs placebo: 6.25 cm Male: 7.07cm vs placebo: 6.39cm	Patient self-report
Skoner 2000	NR/NR/80	Mean standing height at 1 year: BDP: 5.0cm vs placebo: 5.9 cm	NR

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Schenkel 2000	Number of patients reporting adverse events Epistaxis: MFNS 12% vs placebo: 8% Nasal irritation: MFNS: 8% vs placebo: 6% Headache: MFNS: 0 vs placebo: 2% Pharyngitis: MFNS: 0 vs placebo: 2% Rhinitis: MFNS: 0 vs placebo: 2% Sneezing: MFNS: 0 vs placebo: 0	Withdrawals (16) : MFNS: 7 vs placebo 9; Withdrawal due to adverse event (2): MFNS: 1 vs placebo: 1	
Skoner 2000	No unusual adverse events observed	NR; NR	

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Allen, 2002	Randomized, double-blind, placebo-controlled	Children with perennial arthritis found from positive skin test, nasal symptoms at least once daily in past year, normal current growth within 5-95 percentile, normal height growth reflected in at least two height measurements, Tanner Sexual maturity rating of 1 for all classifications. Exclusion: conditions that could require concomitant corticosteroid therapy, use of inhaled, intransal, oral, optical or injectable corticosteroids, or >1% subcutaneous hydrocortisone with 1 month of study, evidence of malnutrition	fluticasone propionate aqueous nasal spray, 200mcg daily vs placebo Study period: 1 year	NR/NR
Holm 1998	Randomized, double-blind, placebo-controlled, parallel Single-center	Patients with perennial allergic rhinitis for at least 1 year. Exclusion: serious/unstable disease,infection of upper/lower respiratory tract, structural abnormalities, nasal surgery >6 months before study, concurrent use of oral/inhaled steroids, intrana	intranasal fluticasone propionate aqueous, 100mcg twice daily vs placebo Study period: 1 year	4 weeks/NR

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Allen, 2002	NR	Growth, measured by stadiometry every 30 days at clinical visit	6 years 34% Female White: 80%, Black: 11%, Asian: 2%, Hispanic: 4.5%, Other: 2%	NR	NR/NR/150
Holm 1998	terfenadine tablets, 60mg as rescue medication	12 clinic visits conducted between 4-6 weeks, nasal blockage, nasal discharge, sneezing, nasal itching, eye irritation assessed by daily diary cards completed for 10 days before clinic visits and investigator at clinical visits	28 years 66.6% Male Ethnicity NR	NR	NR/NR/42

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment
Allen, 2002	40/12/110	Mean Height Measurements: vs baseline With at least 3 months of treatment data: F: 119.0cm vs placebo: 119.0cm At one year of treatment: F: 125.5cm vs placebo: 125.4cm	Patient outcome, self-report
Holm 1998	NR/NR/29	Percentage of patients with symptoms: Baseline vs 1 year: FPANS Mucosal swelling: 23% vs 11% Evidence of crusting: 8% vs 14% Evidence of bleeding: 0% vs 5% Nasal polyps: 0% vs 0% Baseline vs 1 year: placebo Mucosal swelling: 62% vs 37% Evidence of	Patient outcome, self-report

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Allen, 2002	Report of Adverse Events: Any event: F: 12% vs placebo: 12% Epistaxis: F: 9% vs placebo: 8% Nasal irritation: F: 3% vs placebo: 0% Headache: F: 1% s placebo: 1% Gastric upset: F: 0% vs placebo: 1% Nasal burning: F: 0% vs placebo: 1% Nasal soreness: F: 1% vs placebo: 0% Vestibulitis of nose: F: 0% vs placebo: 1%	40;9	
Holm 1998	No major adverse events reported Minor adverse events reported: Total: FPANS: (13)62% vs placebo (12)57% FPANS: Headache: 5 Bronchitis: 3 Epistaxis: 3 Upper respiratory tract infection: 3 Mental depression: 1	NR; 1	

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Study design Setting	Eligibility criteria	Interventions	Run-in/washout period
Cutler 2006	Randomized, double-blind, placebo-controlled, parallel Single-center	Children age ≥2 to <6 yrs with diagnosis of allergic rhinitis in good health (based on medical history, physical exam, ECG and routine lab tests)	mometasone furoate (MFNS) 100µg/day placebo Study period: 6 wks	NR/NR

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled
Cutler 2006	NR	Serum cortisol concentration and urinary free cortisol lels at day 42 (primary endpoint) AEs spontaneously reported	4.0 years 59% male 39.3% Caucasian 55.4% Black 5.3% Othe	Mean height 101 cm Mean weight 18.0 kg	NR/NR/56

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Number withdrawn/ lost to fu/ analyzed	Outcomes	Method of adverse effects assessment
Cutler 2006	4/0/56	NR	Patient self-report

Evidence Table 13. Placebo-controlled trials of harms outcomes

Author Year	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Cutler 2006	Adverse events: MMNS vs placebo Headache: 2/28 (7%) vs 3/28 (11%) Rhinorrhea: 2/28 (7%) vs 3/28 (11%) Abdominal pain: 0/28 vs 2/28 (7%) Irritability: 1/28 (4%) vs 1/28 (4%) URTI: 2/28 (7%) vs 0/28 Ecchymoses: 0/28 vs 1/28 (4%) Skin trauma: 1/28 (4%) vs 0	4; NR	

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Allen 2002 USA	NR	NR	yes	yes	yes	NR	yes	yes, no, no, no
Holm 1998 Netherlands	NR	NR	NR	yes	yes	NR	yes	yes, no, no, no
Skoner 2000	Method NR	NR	no, mean age and mean height in beclomethasone group was significantly greater	yes	yes	yes	yes	Yes, No, No, No

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

					External Validity		
Author, Year Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Allen 2002 USA	yes	yes	no	fair	NR/NR/150	conditions that might affect growth or require concomitant corticosteroid therapy (except for asthma controlled by as-needed Beta-agonists administered on no more than two days weekly), use of inhaled, intranasal, oral, optical, or injectable corticosteroids or >1% cutaneous hydrocortisone within one month of the first prestudy stadiometry measurements and evidence of malnutrition.	4-day screening period
Holm 1998 Netherlands	yes	Not clear	no	fair	NR/NR/42	serious or unstable disease, infection of the uppre and lower respiratory tract, structural abnormalities or intranasal sympaticomimetic therapy, pregnant or lactating women.	4-week placebo run-in
Skoner 2000	No	yes	no	fair	NR/NR/100	Patients taking medications known to affect growth during the study	Washout periods for medications known to affect growth were established, but not reported in abstract

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Allen 2002 USA	no	yes	GlaxoSmithKline supported study	yes
Holm 1998 Netherlands	no	yes	financial support from Glaxo VB, The Netherlands	yes
Skoner 2000	no	N/A	NR	yes

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Schenkel 2000 Abstract	Method NR	NR	yes	yes	yes	yes	yes	No, no, yes, no

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

					External Validity		
Author, Year Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Schenkel 2000 Abstract	no	yes	no	fair	NR/NR/98	None reported in abstract	Washout periods for medications known to affect growth were established based on estimated period of effect and these medications were prohibited during the study, but not reported in abstract. Short courses os either oral prednisone lasting no longer than 7d or low-potencytopical dermatological corticosteroids lasting no longer than 10d were permitted if necessary

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Schenkel 2000 Abstract	no	N/A	NR	yes

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Internal Validity

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination
Cutler 2006	Method NR	Method NR	yes	yes	yes	yes	yes	No,No,No,No

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

				External Validity			
Author, Year Country	**Loss to follow-up: differential/high**	**Intention-to-treat (ITT) analysis**	**Post-randomization exclusions**	**Quality Rating**	**Number screened/ eligible/ enrolled**	**Exclusion criteria**	**Run-in/washout**
Cutler 2006	no	no (~7% excluded from final analysis)	no	fair	NR/NR/56	History of any disorder that might interfere with study evaluation; any local or systemic infection w/in 4 weeks of study; URTI w/in 6 weeks of study; use of prescriotion or OTC drugs other than for AR w/in 2 weeks of study; use of any investigational drug w/in 30 days of study; use of IM corticosteroids w/in 1 yr or oral or orally or nasal inhaled corticosteroids w/in 6 mos of study; multiple drug allergies or corticosteroid allergies; positive hep B surface antigen or C antibody test	NR

Evidence Table 14. Quality assessment of placebo-controlled trials of harms outcomes

Author, Year Country	Class naïve patients only	Control group standard of care	Funding	Relevance
Cutler 2006	no	yes	Schering Plough	yes